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ABSTRACT

Five years have elapsed since the International Conference on Malnutrition, Learning, and Behavior at the Massachusetts Institute of Technology. The present Seminar was held to examine progress since then. The following papers were presented and discussed: "Malnutrition and the Nervous System," Donald B. Cheek, A. B. Holt, and E. D. Mellits; "Lasting Deficits and Distortions of the Adult Brain Following Infantile Undernutrition," John Dobbing; "Some Speculations on Mechanisms Involved in the Effects of Undernutrition on Cellular Growth," Myron Winick, J. A. Brasel, and Pedro Rosso; "Small-for-Dates Offspring: An Animal Model," R. J. C. Stewart; "Empirical Findings with Methodologic Implications in the Study of Malnutrition and Mental Development," Robert E. Klein et al.; "Malnutrition and Mental Capacity," Fernando Monckeberg; "The Influence of Malnutrition on Psychologic and Neurologic Development: Preliminary Communication," Jan Hoorweg and Paget Stanfield; "The Functioning of Jamaican School Children Severely Malnourished During the First Two Years of Life," Herbert G. Birch and Stephen A. Richardson; "Environmental Correlates of Severe Clinical Malnutrition and Language Development in Survivors from Kawshiorkor or Marasmus," Joaquin Cravioto and Elsa DiLicardie; "Ecology of Malnutrition: Nonnutritional Factors Influencing Intellectual and Behavioral Development," Stephen A. Richardson; "Issues of Design and Method in Studying the Effects of Malnutrition on Mental Development," Herbert G. Birch; and, "Nutrition, Public Health, and Education," Jack Tizard. (JM)

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NUTRITION, THE NERVOUS SYSTEM, AND BEHAVIOR

Proceedings of the Seminar on
MALNUTRITION IN EARLY LIFE AND SUBSEQUENT MENTAL DEVELOPMENT

MONA, JAMAICA
January 10-14, 1972

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FOREWORD

Five years have elapsed since the known relationship between malnutrition and the development of brain and behavior was reviewed at the International Conference on Malnutrition, Learning, and Behavior at the Massachusetts Institute of Technology. Since then new studies in the laboratory and in the field have been carried out or begun in many countries. The present Seminar was held at the University of the West Indies at Mona, Jamaica, from January 10 to 14, 1972, to examine this progress and bring together researchers in the field to share their ideas and techniques. The participants were all active investigators from Latin America, the Caribbean, Europe, and the United States. In preparing their papers and discussions to follow the presentations, they were asked to bear in mind the following purposes of the seminar:

1. To review current knowledge about malnutrition and its effect on brain and behavior. Major attention was to be given to developments that had occurred since the publication in 1968 of Scrimshaw and Gordon's *Malnutrition, Learning, and Behavior*, the proceedings of the previous year's conference at the Massachusetts Institute of Technology.

2. To identify and discuss issues and problems in nutrition studies that relate to mental and behavioral development.

3. To enable some of the investigators to present progress reports on their current work.

4. To identify areas and requirements for future research.

5. To consider the implications of present scientific knowledge for public policy and practice, and the role scientists may play in communicating their findings so as to be helpful to policy makers and concerned citizens.

Dr. David Picou conceived the Seminar, and Drs. Herbert G. Birch, M. Martins da Silva, Picou, Stephen A. Richardson, and John Waterlow developed its structure and program. The number of participants was small but included investigators from many centers where research is being conducted on various aspects of the Seminar's topic.

The Government of Jamaica, the Wellcome Trust, and the Pan American Health Organization generously gave financial assistance, and the University of the West Indies and the University Hospital graciously provided the conference facilities.

Authors and rapporteurs revised their presentations and reports after the Seminar. The editors have tried to ensure that the rapporteurs' reports reflected the discussions at the end of each session.

CONTENTS

Welcoming Speakers, Participants, and Invited Guests vii
Program Committee and Secretariat ix

Session I. Malnutrition and the Nervous System in Animals and Man

Malnutrition and the Nervous System *Donald B. Cheek, A. B. Holt, and E. D. Mellits* 3
Lasting Deficits and Distortions of the Adult Brain Following Infantile Undernutrition *John Dobbing* 15
Some Speculations on Mechanisms Involved in the Effects of Undernutrition on Cellular Growth *Myron Winick, J. A. Brasel, and Pedro Rosso* 24
Small-for-Dates Offspring: An Animal Model *R. J. C. Stewart* 33
Summary of Session I *Herbert G. Birch* 38

Session II. Functioning of Children Malnourished in Infancy or from Disadvantaged Social Backgrounds

Empirical Findings with Methodologic Implications in the Study of Malnutrition and Mental Development *Robert E. Klein, Jean-Pierre Habicht, Charles Yarbrough, Stephen G. Sellers, and Martha Julia Sellers* 43
Malnutrition and Mental Capacity *Fernando Mönckeberg* 48
The Influence of Malnutrition on Psychologic and Neurologic Development: Preliminary Communication *Jan Hoorweg and Paget Stanfield* 55
The Functioning of Jamaican School Children Severely Malnourished During the First Two Years of Life *Herbert G. Birch and Stephen A. Richardson* 64
Environmental Correlates of Severe Clinical Malnutrition and Language Development in Survivors from Kwashiorkor or Marasmus *Joaquín Cravioto and Elsa DeLicardie* 73
Summary of Session II *Jack Tizard* 95

Session III. Ecology of Malnutrition

Ecology of Malnutrition: Nonnutritional Factors Influencing Intellectual and Behavioral Development *Stephen A. Richardson* 101
Summary of Session III *Joaquín Cravioto* 111

Session IV. Methodologic Issues in Malnutrition Studies

Issues of Design and Method in Studying the Effects of Malnutrition on Mental Development *Herbert G. Birch* 115
Summary of Session IV *Robert E. Klein* 129

Session V. Future Research Directions

Summary of Session V *Herbert G. Birch* 133

Session VI. Social and Administrative Problems

Nutrition, Public Health, and Education *Jack Tizard* 139
Summary of Session VI *Robert Cook* 147

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Session I

MALNUTRITION AND THE NERVOUS SYSTEM IN ANIMALS AND MAN

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E. K. Cruickshank

Rapporteur

Herbert G. Birch

MALNUTRITION AND THE NERVOUS SYSTEM[1]

Donald B. Cheek, A. B. Holt, and E. D. Mellits[2]

The present paper reviews the subject of malnutrition and the nervous system in animals and man. Our own interests over the years have focused more on the role of hormone and nutrition in cellular growth of the soma (*16*, *17*), and the nervous system has been of recent interest because of our work on fetal growth. During the last decade, a great deal of interest in the role of nutrition in brain growth has arisen. Three years ago, Winick, realizing that millions of children were suffering from undernutrition and taking cognizance of the results of progress, made the following prediction: "Both animal experiments and human studies suggest that a critical period of brain growth may exist during which malnutrition even in a mild form and even for a short time, may produce irreversible damage. This critical period appears to be before birth and during early postnatal life" (*80*). Dobbing had a similar message: "The possibility that undernutrition in early life may permanently reduce the intellectual capacity of men and women has become increasingly recognized in recent years. In pediatrics we must now be much more concerned about undernutrition at certain vulnerable stages in development having long-term sequelae which may be irreversible in spite of most strenuous attempts at rehabilitation" (*29*).

[1] This work was supported by the National Institute of Child Health and Development Grant HD-00126-08, National Institutes of Health, Bethesda, Maryland.

[2] Johns Hopkins University, Baltimore, Maryland, USA.

These are profound statements, which not only make all branches of the medical world spring to attention but lie heavily on the minds of the administrator and politician.

The evidence for these statements arises from work in animals and man. It is important to review this evidence briefly. One may consider information on rodents (small mammals), pigs (large mammals), and monkeys and humans (primates). We intend to deal mainly with chemical information.

Nutrition and the Rodent Brain (the small mammal)

It has been known for 50 years that restricted nutrition in postweaning rats does diminish brain size or brain weight (*48*). The findings of Eayrs and Goodhead (*32*) confirmed the thinking. The early experiments of Widdowson (*75*, *76*) showed that more severe effects arose if restriction extended from an earlier time or from one to 21 days.

In 1964, Dobbing (*27*) reported on the influence of early nutrition on the development and myelination of the brain. Later he and Widdowson (*28*) studied the effects of rehabilitation on myelination in deprived rats. The changes produced by restricting diet between the third and 11th weeks of life were reversed at 19 weeks. In 1965, Benton and coworkers (*8*) showed that restricted nutrition during the preweaning period resulted in deficits of brain weight, lipid content, phospholipid, cholesterol,

and cerebroside. Refeeding reversed all of these changes, however.

Platt and coworkers (*62*) drew attention to histologic changes in the neurone and neuroglia of protein-restricted rats. Such degenerative changes did not reverse after protein feeding.

Nucleic acid analyses by Winick and Noble (*78*) of brain tissue showed that restricted nutrition in the first 21 days of life caused an abrupt cessation of cell division (DNA increase). In the postweaning period, the reduction of DNA and the deficit in cell number was permanent, provided the insult had occurred during weaning. If the insult had been inflicted after 21 days, no changes persisted. Dickerson and Walmsley (*24*) found no changes in cell number resulting from food deprivation after 21 days. If nutritional status is restored before the 10th day, however, effects can be reversed (*79*).

Other workers made similar findings. Culley and Mertz (*21*) found in 1965 that undernutrition from five to 20 postnatal days caused a sustained reduction in brain weight and phospholipid, cholesterol, and cerebroside content. Guthrie and Brown (*42*) made similar findings, and Culley and Lineberger (*22*) showed that if malnutrition was extended to 17 days of postnatal life, irreversible changes occurred. Chase and coworkers (*11*) found that the incorporation of sulfatide into the myelin of rat brain was markedly reduced by malnutrition during the first three weeks of postnatal life. The extensive studies, chemical and histologic, of Bass and coworkers (*6, 7*) focused on the somatosensory area of the rat cortex. They showed significant arrest of brain growth as a result of food restriction from one to 21 days. Not only was there delayed growth of the cerebral cortex, but the migration of cells was delayed and undifferentiated cells remained in the white matter. There was a great decrease in dendritic proliferation.

Despite the multiple studies showing changes in the cerebrum or the whole brain during and after the weaning period, the balance of evidence indicates that the cerebellum is the most affected in rats. This was the conclusion of Culley and Lineberger (*22*), and was clearly shown by Chase and coworkers (*12*) in their rat studies. Winick also noted that in rats deprived for a short time, or for the first nine days only, the cerebellum was the organ affected (*79*). Howard and Granoff (*47*) found the greatest change in mice deprived in the weaning period in the cerebellum. In the rat it is the cells of the cerebellum that are most rapidly dividing at that time (*1*). Hence, substrate deprivation affects that organ most.

The question arises whether calories or proteins are lacking in these animals. Careful work by Miller (*57*) of the Massachusetts Institute of Technology, using artificial feeding, has shown that the central nutritional factor missing is protein.

Bearing in mind the pattern of cell growth in the rodent, as shown by Enesco and Leblond (*33*) and by Winick and Noble (*77*), namely hyperplasia in utero, hyperplasia and hypertrophy postnatally, and finally, hypertrophy per se, it would seem reasonable to agree with Winick (*80*) that not only is the extent or duration of nutrition important, but the age of the animal at the time of insult or rehabilitation is critical. Thus, we can look for critical periods or times when cell multiplication is greatest, and at those times we may suspect that substance restriction will be highly deleterious and therefore may influence subsequent growth. Dobbing (*29*) has emphasized the vulnerable period as being the period of the brain growth spurt, the period during which it is passing through the rapid phase of its sigmoid growth trajectory. This is the period when minimal food restriction might be expected to produce maximal alteration in brain growth. He has emphasized that nothing will delay the "scheduled spurt" of growth in the brain, though the intensity of the spurt may be diminished by deleterious factors.

We have so far reviewed the information on rodents and mainly the effects of protein restriction on brain growth during the first 21 days of postnatal life. One might confidently expect that dramatic changes in rat brain growth occur during this period. That is indeed the case. Rats are born with only 20 per cent of their expected brain cells present, and a critical period may be defined at nine to 10 days.

As shown by Brasel and coworkers (*9*), at seven to eight days there is a marked increase in DNA polymerase activity. This increase is followed by a doubling within three to four days of DNA and brain cells, while from 10 to 17 days there is a great acceleration. The full complement of cells is reached. Surely this is a critical period. At the same time, as shown by Millichap (*58*) and Ashby (*2*), the carbonic anhydrase present in the neuroglial cells (*39, 40, 51*) also rises precipitously at nine days. Chase and coworkers (*11*) have shown accelerated SO_4 incorporation, which indicates active myelination.

We can now understand why experiments including our own (*14*) with food or protein restriction in rats from one to 10 days old do not produce any later changes in brain chemistry. Indeed, it can also be pointed out that the brain changes that result from thyroid ablation in newborn rats can be reversed if hormone therapy is given before the 10th postnatal day (*38, 52*). The intensity of the insult must also be important, as we shall discuss later. It is now pertinent to review the situation in rats in the prenatal period.

Zamenhof and coworkers (*84*) showed that when pregnant rats were fed 8 per cent protein, the offspring had a reduction in brain DNA and protein content. Zeman and Stanbrough (*85*) confirmed this, while Zeman (*86*) later found that adequate nutrition in the immediate postnatal period reversed such chemical changes.

Thus, the balance of evidence indicates that in the rat maternal food restriction limits available substrate for the fetus, and though only 20 per cent of the brain cells are due to appear during fetal life, the nutritional stress is sufficient to interfere with cell development. If adequate nutrition is instituted postnatally, no chemical changes persist. Nutritional insult to the weanling rat would appear to be of greater consequence than for the fetal rat. Studies of behavior in deprived rats support this thesis (*3*). Conversely, as shown by Chase and coworkers (*13*) in the guinea pig, in which almost all cell multiplication occurs in utero (*30*), food restriction to the mother produces changes in the cerebellar DNA, protein, and lipids of the fetus. Adequate feeding postnatally does not totally reverse the diminution of cellularity in the adult cerebellum.

Nutrition and the Pig Brain (large mammal)

At birth the pig weighs only 6 kg but as an adult it weighs 200 kg, a 30-fold increase. Hence, postnatal nutritional deprivation should strongly affect somatic growth. The DNA in the forebrain, cerebellum, and cord increases maximally just before birth, and cell multiplication continues to 12 weeks postnatally (*25*). There is a peak in the rate of DNA increase five weeks before birth. Pond and coworkers (*63*) gave pregnant pigs a protein-free diet but offered an adequate diet postnatally. In the adult phase the offspring showed no reduction of DNA in the cerebrum and only a borderline reduction in RNA. Psychologic and intellectual changes at first thought to be significant (*4, 54*) have since been found to be heavily influenced by environmental factors (*5, 36*).

Dickerson and coworkers (*26*) restricted nutrition in pigs for the first year of life—a severe stress—and then refed the animals for two more years. The cellular content of the brain did not reach expected levels.

Evidence with respect to pigs is limited, but it would appear that the fetal brain is highly resistant to maternal protein restriction and that severe and prolonged protein restriction is neces-

sary to produce chemical changes in postnatal life.

Nutrition and Brain Development in Man

(*a*) *Normal brain growth*

The human has one-third of his eventual number of brain cells at birth, which is less than that of the guinea pig and monkey but greater than that of the rat. The rate of brain-weight increase in rat, pig, and man has been compared by Davison and Dobbing (*23*). The peak in man is reached shortly before birth, but that in the rat is postnatal. The work of Dobbing and Sands (*31*) and of Dobbing (*29*) reveals that if the cerebral DNA is considered from 10 weeks' gestation to three months postnatally, one can draw a curve to fit the points indicating a fourth-order relationship (a sigmoid curve followed by a straight line). It is believed that the first spurt (from 15 to 20 weeks) is neuronal and the second (from 25 weeks on) is neuroglial, while the complete complement of cells is reached two years postnatally. We have analyzed these data for whole brain (*18*) and more recently for cerebrum by polynomial regression analysis. We obtain a strong linear fit for whole brain and a quadratic fit for cerebral DNA. No evidence of a higher fit up to a fifth-order relationship has come to hand. If there is some biologic reason for regarding the period 10 to 22 weeks as separate (as Dobbing has divided his data (*29*)) and 22 weeks to three months postnatally as a second period, then the relationship would hold as stated. By considering the increments in brain DNA as a percentage of the adult value per unit of time (five-week periods), Dobbing has shown two peaks of cell growth, the major one being three months postnatally, which may correspond to a period of extensive myelination and presumably is to be regarded as a vulnerable period.

We do not interpret the data as does Dobbing. If we apply the technique of Mellits (*56*) to the strong quadratic relationship obtained for cerebral DNA against time, it should be possible to fit two intersecting straight lines in place of the quadratic. The point of intersection can have significance insofar as it indicates a period in which there is a change in the rate of growth (*56*). If we undertake this procedure, a break is obtained at 32.8 weeks' gestation. If we also inspect the extensive data of Schultz and coworkers (*66*) on brain weight (1,193 brains) and plot these data as a percentage of increase in weight against conceptual age, we find two peaks. one at 32 weeks' gestation and another five months postnatally (Figure 1). The data of Coppoletta and Wolbach (*20*) yield the same information if plotted.

If one reassesses Dobbing and Sands' data on brain DNA content (*31*), they may be expressed

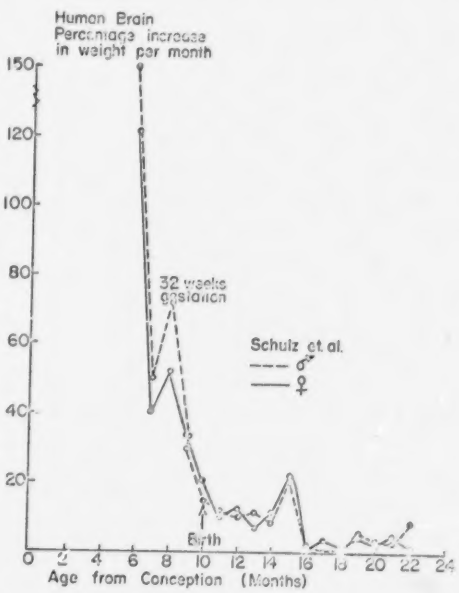

Figure 1. Brain growth is expressed as the percentage of increase per month from conception. The data are taken from the work of Schultz and coworkers (66). Note that at eight months' gestation (32 weeks) there is a decided peak of change in brain growth. A second peak is also described at five postnatal months (20 weeks postnatally). The same second may be found if the data of Coppoletta and Wolbach (20) are similarly examined.

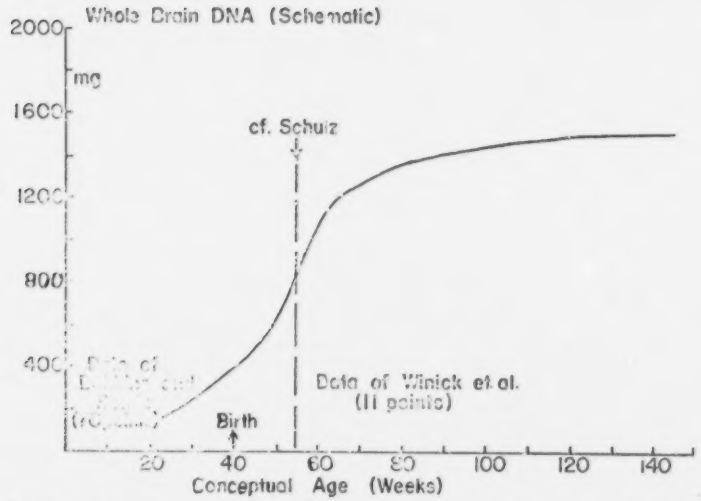

Figure 2. Composite schematic graph showing the growth of whole brain DNA. From 20 weeks' gestation to 15 weeks postnatally the data of Dobbing and Sand have been used (31), and from that time until 110 weeks postnatally, the recent data of Winick and coworkers (81) have been employed. From available evidence one would suspect that the steepest rise is at 20 weeks postnatally or at the time shown in Figure 1.

as a linear or a quadratic function up to 55 weeks (conceptual age) (*18*) (Figure 2). At 55 weeks, data from Winick and his coworkers (*81*) may be used. (Earlier data are different (*18*)). If the line of best fit is drawn subjectively (Figure 2), it becomes clear that from 15 to 20 weeks postnatally there is a period of maximal cell growth. This result is different from the earlier thinking of Davison and Dobbing (*23*). These remarks are made not to contradict their excellent work, but to draw attention to an alternate interpretation of their data.

(b) Malnutrition and human brain growth

Both kwashiorkor and marasmus exert deleterious effects on brain growth. Brown (*10*) reported a reduction in brain weight and Garrow (*37*) found reduced ^{40}K radiation from the brain in living infants and the restoration of that count after rehabilitation. Winick and Rosso (*82*) analyzed brains from marasmic children who died during their first year of life to determine RNA, DNA, and protein content. The early gestational history of the infants was not known, but deficits in the chemical markers were found and brain growth arrest was demonstrated. Fishman and coworkers (*35*) reported a reduction of lipids, cholesterol, and neuraminic acid in the brains of infants who died of malnutrition between two and 22 months of age.

Available data about normal postnatal values for DNA, RNA, and protein in the human brain from three to 12 months are meager, and discrepancies in data between laboratories exist (*18*). Dobbing notes that losses of RNA and protein occur following death (*29*). Winick and his coworkers (*82*) showed that the DNA content of the normal human cerebrum reached a constant value six months postnatally, which is not in accord with Dobbing's data (*29*). The marasmic infant had significantly less cerebral DNA. Similar findings were made in the cerebellum, and brain lipids were reported to be reduced (*81*). The important question is

whether this growth arrest in the living infant is reversible.

Psychologic studies of malnutrition in infants are numerous and their results indicate mental impairment ((67) for review), but the investigator has to separate the effects of the environment from the effects of nutritional restriction as such (5, 36).

With respect to prenatal malnutrition in the human, the information relating to wartime starvation in Holland is often cited (71). There the intake was 400 calories per person per day. Newborn infants were decidedly retarded in growth. Those infants (now 27- and 28-year-old adults) have been thoroughly investigated by Dr. Z. Stein of New York (72), who found no deficit in intelligence. Severe placental insufficiency as seen in human parabiotic twins is known to cause changes in the IQ of one twin (19).

The evidence with respect to the human thus indicates an arrest of brain growth if nutritional restriction occurs. Whether intelligence is impaired is not clear. Maternal protein-calorie deprivation would not appear to alter the intelligence of the offspring.

Nutrition and the Brain of Macaca mulatta

We have recently inspected the changes in DNA, RNA, protein, cholesterol, ganglioside, water, and chloride in the cerebrum and cerebellum of the rhesus monkey from midgestation (80 days) until term (160 days) and for 30 days postnatally. From midgestation the cerebral weight, and DNA, RNA, protein, and ganglioside content rise as a slight sigmoid curve and reach adult values at or soon after 30 days postnatally. The RNA:DNA ratio rises and reaches a peak at birth. The increment in ganglioside (NANA) is prominent from 120 days to birth, when a steady value is obtained. Cholesterol content increases later and continues to increase well into postnatal life. The activity of carbonic anhydrase activity is markedly increased immediately after birth.

The growth of the cerebellum is, of course, entirely different. The concentration of DNA increases while that of the cerebrum decreases with time, as others have found (55) (Figures 3 and 4). This organ continues to grow and even four months postnatally has not reached adult levels. The DNA, RNA, and protein reach adult levels 80 days postnatally, but cholesterol deposition must continue to increase well into postnatal life. Carbonic anhydrase in the cerebellum increases markedly after birth, as with the cerebrum. These data will be reported separately (46). For the cerebrum, the biggest surge forward in cellular growth would appear to be from 80 days and for the cerebellum from 120 days (Figures 1 and 2). The early attainment of adult levels in the cerebrum (30

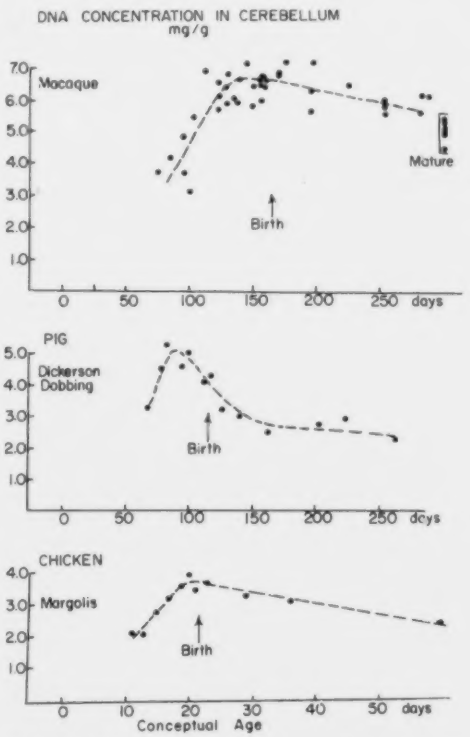

Figure 3. Changes in cerebellar DNA concentrations in the monkey, pig (25), and chicken (55) during gestation and the postnatal period. Note the comparison.

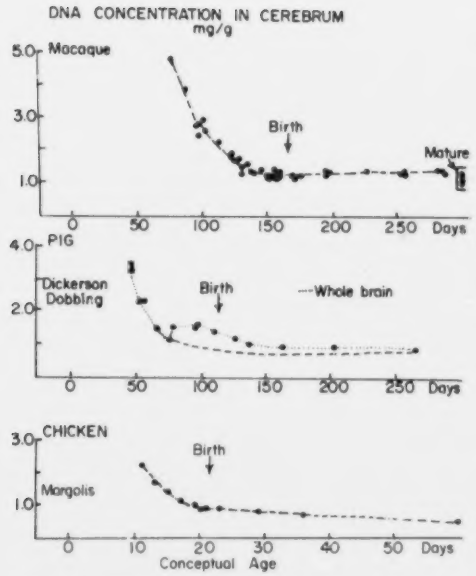

Figure 4. Changes in DNA concentration in the cerebrum of the monkey, pig (25), and chicken (55) during gestation and the postnatal period.

postnatal days) would indicate that critical periods—if they exist—would be in intrauterine life.

Two laboratories have studied the effects of postnatal protein restriction in monkeys, and our own laboratory is now studying the effects of maternal nutritional deprivation on the monkey fetus.

Ordy and coworkers (*60*) gave a 3.5 per cent protein diet to the infant monkey from three to nine months postnatally without producing any change in brain weight. Kerr and coworkers (*50*) produced growth arrest in monkeys from one to seven months of age with a protein-deficient diet. Many of the infants died. Brain weight was not reduced in general, but changes in the liver, myocardium, and intestines were significant. The infants were then refed the control diet from seven months to one year. Catch-up growth occurred and was eventually complete anthropometrically. Head circumference was normal. Drs. A. Deets and P. Harlow of the University of Wisconsin have found no subsequent behavioral or psychologic deficits in these primates (personal communication).

In the rhesus monkey, cerebral cell number is almost complete at one month, and certainly so by three months. Myelination is still in progress, as is the growth of the cerebellum. It can be argued that nutritional restriction in the prenatal period will alone be the time to produce permanent cerebral changes in the monkey.

By removing the secondary placenta of the fetal monkey at 100 days' gestation, we did produce a half-sized term fetus (*44*, *59*). Since the placenta is responsible for the transfer of substrates, we believe that this represents a good example of fetal malnutrition. We have been able to show in the cerebellum, but not in the cerebrum, a reduction in protein and DNA content and a borderline change in RNA, but we do not know whether these changes are reversible or not.

Our second approach is to study brain growth after restricted maternal nutrition during pregnancy. This work is in collaboration with the National Institutes of Health, and in particular with Drs. London, Weiss, Ellenberg, and Bieri. We are studying the effects of severe protein and calorie restriction on the pregnant rhesus monkey. The intake of calories and protein has been kept to about one-third of normal. The weight loss of these pregnant animals ranges from 0.5 to 1.0 kg. A few control and experimental fetuses have come to hand and have shown us little chemical change. A decrease in cholesterol, which could well be reversible (*28*), would appear to exist, and also a decrease in protein:DNA, especially in the cerebellum. More work is necessary before these findings can be substantiated.

Implications

It has been shown that development of the rat brain is highly susceptible to nutritional deprivation between seven and 17 days, when cellular growth is remarkable. The abnormal

changes persist. Protein restriction during pregnancy does cause changes in cell number and in protein accretion in the fetal rat brain, but these changes are reversible (*86*). This is not so for the guinea pig, in which cell multiplication is almost completed during intrauterine life. Nutritional deprivation during pregnancy interferes with subsequent growth of the cerebellum postnatally (*13*).

By implication, one might anticipate that insults would be significant for the subhuman primate during pregnancy and would also mainly affect the cerebellum, since most of the brain cell growth is in utero and cerebellar growth again is still in progress during the postnatal period. It is probable that for the human the period around five months postnatally is critical. No evidence exists, however, to show whether brain changes do or do not persist in the primate, although it is clear that some growth arrest occurs. We do not know whether refeeding will reverse the changes, but the observations of Stein and coworkers (*72*) would certainly suggest that the cerebral cortex does not suffer any changes because of nutritional deprivation during pregnancy. Moreover, one must keep in mind that primate cell growth is much slower than in nonprimates (*61*), so that the insult would have to be disproportionately greater to produce a change comparable to that found in rats. It is also true that the smaller the mammal, the greater the litter size (*53*) and the faster the rate of fetal tissue accretion (*18*). It is for these reasons that we suggested that the syndrome of growth arrest in the brain without reversal is mainly a condition present in small mammals, in which metabolic rate, protein turnover, and nutritional requirements are disproportionately higher (*18*).

While obvious differences do exist in primate growth relative to nonprimate growth, it is also true that events in brain growth are very similar. To illustrate this point we have drawn Figures 5, 6, and 7. The percentage increases in the DNA content and brain weight for the rat, guinea pig, and man are shown. The time at which stability of brain weight occurs is taken. This is plotted as 100 per cent, and on the abscissa 0 to 100 per cent represents time from conception to stability of brain weight. The ordinate represents the percentage of weight or of DNA reached relative to maturity. For the human brain, the assumption was made that cell growth occurs as shown in Figure 2. We assume that the mature level of DNA in the human whole brain is 1,500 mg (*81*). The similarity of Figures 3, 4, and 5 is obvious, and the maximal periods of cell growth may be seen. For the rat, however, the spurt in cell growth (from 50 to 90 per cent of expected) is indeed rapid. This would support the inference that the critical period in the rat is more remarkable.

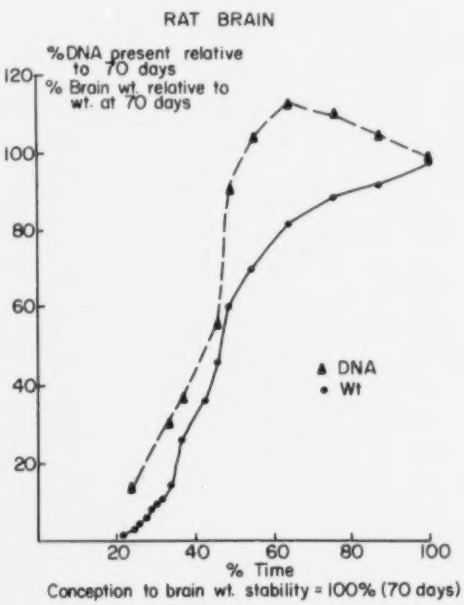

Figure 5. The period from conception until the brain reaches a stable weight is documented as 100 per cent. In the rat this period is 70 days from conception. The ordinate shows the percentage of DNA or percentage of weight relative to the stable level reached at any particular time. Note the steep climb in the rat that occurs halfway through development. Points are calculated from available data (*9, 70*).

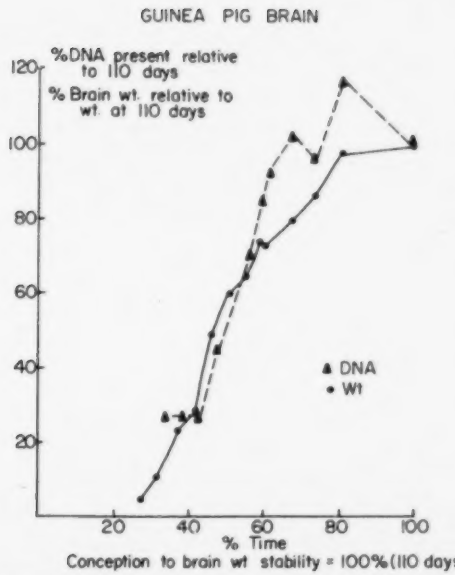

Figure 6. Figure 6 is similar to Figure 5 but plotted for the guinea pig, whose brain weight stability is reached at 110 days from conception. The rate of DNA accumulation is not as fast as the rat's. Points have been calculated from available data (30).

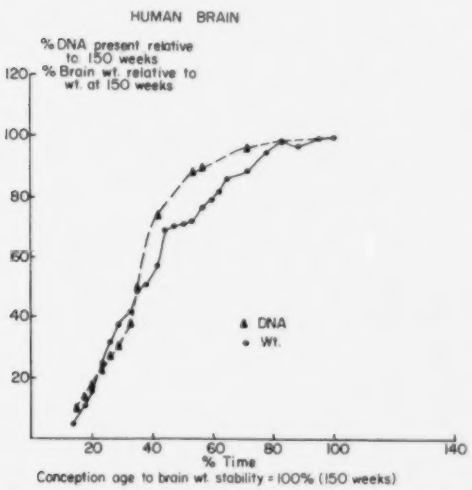

Figure 7. This figure is again similar to Figure 5 but is plotted for the human. Stability of brain weight is taken as 150 weeks from conception. Note that DNA increase rate is again not as rapid as for the rat. Points have been calculated from available data (20, 31, 65, 66, 81).

Our own work has shown us that the cerebellum is the organ mainly affected in the primate. Although this work is incomplete, it could be that no lasting cerebral or cerebellar defects will unfold because of protein restriction in the prenatal period.

Workers studying psychologic and behavioral changes due to undernutrition are becoming more convinced that environmental deprivation (stimulation) is the key factor. Undoubtedly, altered reaction to stimuli, emotional instability, and withdrawal are characteristic of nutritionally deprived subjects (5). If lack of stimulation is added to protein deprivation, then mental retardation may be expected. Whether such is reversible is not known.

Seresi and coworkers (68) have shown that norepinephrine and serotonin levels are reduced in the brain of rats deprived nutritionally from one to eight days. Shoemaker and Wurtman (69) find that the brains of the offspring contain less dopamine and norepinephrine if the lactating mother receives a diet restricted in protein. Food intake stimulates insulin secretion, which in turn elevates amino acid levels including that of tryptophan, which sequentially elevates the level of serotonin.

Our earlier work drew attention to the failure of proper insulin release in protein-deficient rats or infants (41, 43). It is possible that insulin plays some role in brain growth (45).

Whether growth hormone performs any role in brain growth is also not clear. Some evidence exists to show that it does (15, 38, 52, 83). Observations by Taplin (74) indicated that the number of acidophil cells in the pituitary and the weight of the gland are linearly related to the weight and size of the mature rat following restricted feeding early in postnatal life. Stephan and coworkers (73) found that the offspring of underfed dams have smaller pituitaries containing lower concentrations of growth hormone. In other words, it would appear that hormonal mechanisms adjust to growth processes but nutritional intake is the

key or leading factor (*49, 64*). It is conceivable that an imbalance of the sympathetic nervous system and reductions of hormones important to growth are also crucial to the development of these brain changes. Perhaps these mechanisms are just as important as critical periods since, for example, we find that exposure of rats to 12 per cent oxygen from one to seven days postnatally later produces extensive changes to the brain, while nutritional deprivation during the same, noncritical period has no effect (*14*). Moreover, we have found in unpublished work that thyroid hormone is fundamental to brain growth during fetal life. (It is known to be important for postnatal brain growth.) The role of this hormone may well be important with respect to brain growth and protein deprivation.

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LASTING DEFICITS AND DISTORTIONS OF THE ADULT BRAIN FOLLOWING INFANTILE UNDERNUTRITION

John Dobbing[1]

The question whether undernutrition during certain stages of brain development contributes to lasting behavioral changes is now attracting increasing attention from research workers in many disciplines. Among those primarily interested in the human implications of the problem, inquiry has centered largely on severely malnourished babies in starkly poor communities, usually but not always in developing countries. It has also impinged on the general pediatric concern for the fate of low-birth-weight babies, especially those of retarded intrauterine growth, and any other babies whose growth may be impaired, including those with metabolic errors, congenital anomalies, endocrine disturbances, chronic hypoxia, long-term exposure to growth-retarding drugs, or any syndrome that includes growth retardation in its consequences.

The question being asked is deceptively simple for the unwary, and many of the more responsible workers in the field are dismayed at the readiness with which it is sometimes overdramatized. The question whether early malnutrition causes mental subnormality or mental retardation or brain damage is, in their view, wrongly posed. Rather it should be asked whether undernutrition or growth retardation, among the multitude of other important early environmental factors, can be identified as a contributor to the algebraic sum of those influences that determine adult "attainment." Efforts to answer this more realistic, but much more difficult question must attempt to isolate the variable of nutrition experimentally, and this of course is strictly impossible.

The present paper will examine the proposition that there are periods of heightened vulnerability in the physical development of the brain, during which growth retardation results in long-lasting and detectable distortions and deficits in adult brain structure. This will necessarily be established in animal species before an attempt is made to extrapolate the idea to our own. Some evidence for the validity of such extrapolation will be discussed.

"Vulnerable-Period" Pathology

Developmental neuropathology has hitherto been exclusively concerned with lesions, structural or biochemical. The former have been either first-trimester teratologic malformations or last-trimester focal destruction through such agencies as hypoxia, hypoglycemia, hyperbilirubinemia, focal hemorrhage, or trauma. Biochemical "lesions" have by contrast been diffuse and identifiable either histochemically (the lipidoses) or not (the inborn errors).

The new pathology proposed here shows none of these features, and will often not even show related physical signs. It consists of quantitative disorders of the brain's growth program

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resulting in easily detectable differences in adult brain structure, but none of these would be revealed by orthodox neuropathology. Neither the very rare nutritional condition of Wernicke's encephalopathy nor such lesions as those of vitamin A deficiency form part of the new pathology, though it is possible that some forms of microcephaly (e.g., in rubella) may be allied with it. An important possibility—though it is no more than that—is that some cases of hitherto unclassified mental retardation may show such quantitative, rather than "lesion," pathology.

The science of developmental nutrition recognizes three important parameters of undernutrition apart from its specific nature. These are its severity, its duration, and its timing, and they are interrelated. The importance of the third factor (the age at which undernutrition occurs) has given rise to the idea of transient periods of heightened sensitivity which have some apparent resemblance to sensitive periods during the development of behavior. Largely because of the need to imply both lasting distortion and lasting deficit, the term "vulnerable" has been used rather than the more academic terms "critical" or "sensitive" period.

The basis of the vulnerable-period hypothesis (*11*) is best illustrated by a clear-cut finding in rats that if bodily growth is retarded at the time of the brain growth spurt, there is a resulting growth deficit that resists subsequent nutritional rehabilitation. There are permanent deficits of both brain and bodily growth attainment, and in the brain at least there is some permanent structural distortion as well as deficit. There is good emerging evidence that the principle is valid for other species, including man.

There is an apparent dependence of good bodily growth on the achievement of a satisfactory brain growth spurt. The bodily growth spurt is later in all species than that of the brain, and is not itself "vulnerable" in the above, lasting sense. Nutritional retardation of bodily growth at this later stage is fully recoverable on restoration of a good diet (*22*), and even severe starvation in the adult produces no lasting detectable effects on the brain (*12*). Whether growth retardation before the brain growth spurt has lasting structural effects is less clear, although by gross measurement these have been too small to detect in the brain (at least when growth is retarded to the extent commonly occurring in humans), just as there are no obvious changes after severe adult undernutrition.

In its originally proposed form (*11*), the period of vulnerability was considered to be the whole period of the brain growth spurt to be described below. A second and overlapping hypothesis (*23*) can also be applied to all other tissues. It was discovered that during their post-organogenetic growth all tissues pass through a period of cell division followed by one of growth in cell size. Undernutrition during the former phase, but not during the latter, permanently reduces growth attainment in all tissues.

There can be no question that this latter is a basic law for catch-up potential throughout the body, but it may nevertheless be unsatisfactory when applied to those aspects of brain development that may be functionally important. For example, glial mitosis occurs later than neuronal mitosis, and glia eventually outnumber neurons heavily. Most experimental proof of the vulnerability of "brain cell" mitosis has been confined to the later phase of glial multiplication, which happens to occupy the first part of the brain growth spurt. Most of the lasting "brain cell" deficit in these experiments must therefore be glial, and it seems unlikely that a numerical glial deficit will be functionally important. It is even possible that a numerical neuronal cell deficit would not be very significant for brain function compared with a deficit, for example, in subsequent dendritic branching and in the establishment of synaptic connections. These later and probably more important features of neuronal growth are not mitotic events. They are the brain's equiva-

lent to growth in cell size, and it is possible that such postmitotic events within the brain growth spurt are also vulnerable. Finally, the technique of expressing average cell size as a protein: DNA ratio must surely be less meaningful for neurons, with their enormously long cytoplasmic extensions, than for a homogeneous mass of liver cells.

The phrase "growth spurt" is derived from the sigmoid trajectory of most organ or whole body growth. It is simply the transient period of high growth velocity. In the brain it is found in all mammalian species examined and represents phases of brain development similar from one species to another. Only the occurrence of birth shows interspecies variation (*11*): in the rat the growth spurt is a postnatal event (*17*), in the guinea pig it is prenatal (*14*), and in pigs (*10*) and people (*13*) it is both pre- and postnatal. Normal birth has no significance for most growth programs including that of the brain. Thus there are obvious pitfalls here for those wishing to use animals to investigate "fetal" or "postnatal" brain growth unless the species is carefully chosen and the timing of the brain growth spurt in that species known.

The brain growth spurt begins at about the time neuroblast multiplication ends and the adult number of neurons has already been almost achieved. This is toward the end of the second human (fetal) trimester (*15*) and in the first postnatal days of the rat. It ends with the end of the major period of rapid myelination, at about two years of human postnatal age (*18*) and at about 25 days in the rat (*17*). In very general terms the velocity curve of increments in brain wet weight encompasses the whole period, except perhaps for the later stages of rapid myelination. The major easily detectable events, apart from an increase in size, are an almost explosive multiplication of oligodendroglial cells (*5*) followed by a period of intense lipid synthesis related to myelination (*7*). There are large and sometimes sudden changes of enzyme activity (*1, 3*). Tissue water falls reciprocally with the rise in brain lipid (*17*). Sodium and potassium move rapidly toward their adult values (*8*). Perhaps more importantly, but less easily measured, the growth spurt includes the growth and branching of dendritic processes and the establishment of interneuronal connections. These are held to be plastic to some extent in the adult, and it would be surprising if they were not even more so during development.

Of course it is grossly facile to attach functional significance to the vulnerability of the growth-spurt complex as described above. Some of the oversimplifications will now be enumerated.

First, neurobiologists have only measured parameters that are comparatively easy to measure. No one knows what to measure as a physical index of important aspects of higher mental function. Certainly cell number, brain size, degree of myelination, and so forth are no more than tangible examples of structural characteristics that, by analogy, may possibly react in a manner similar to whatever structures actually do matter.

Further, developmental processes in the brain occur at different times in different regions and at different rates. There is a highly organized temporal and spatial sequence, and it is likely that there is a differential regional vulnerability related to the normal rate and timing in any particular region. One clear example is the differential vulnerability of the cerebellum, which will be described later. This part of the brain grows more rapidly than other parts and is therefore more specifically affected by growth retardation (*9*). Some of its neurons divide later than most (*4*), and they are therefore differentially selected by later growth retardation (*16*).

Experimental Designs

Experimental studies of nutritional deprivation early in life have often been on rats. It has

been convenient that the brain growth spurt in this species is largely confined to the suckling period. One of the following four nutritional procedures has usually been employed: maternal undernutrition or malnutrition, restriction of suckling time, and rearing in large litters. Maternal undernutrition is achieved by feeding the mother a restricted quantity of a good-quality food daily, whereas in the case of maternal malnutrition, the rat has access to an unlimited supply of an unbalanced diet, often low in protein and consequently high in some other constituent, usually carbohydrate. Restriction of suckling time necessitates regular separation of mother and young so that normal feeding opportunities are curtailed. These three techniques usually involve standardization of litter size at birth. The large-litter method requires that two or more mothers give birth within a short space of time. Young are removed from their mothers and randomly assigned to an abnormally large or small litter. Mother rats or mice would be given large litters of 15 to 20 young.

The desired timing of the nutritional restriction to some extent determines the method of deprivation to be used. Obviously the restricted suckling and large-litter procedures are applicable only to the suckling period, whereas dietary restriction of the putative mother may begin even before she has conceived.

Information on the effects of diet on milk composition is scanty for both humans (*20*) and laboratory animals (*21*). What evidence there is suggests that both protein and calorie restriction suppress milk yield without appreciable alteration in quality. Hence the nutritional effect of the four methods of deprivation on the suckling animal is probably similar.

Some Lasting Effects of Early Growth Retardation

Provided the brain growth-spurt period is carefully selected, it is only necessary to retard bodily growth rates toward the lower limits of the "normal" range to produce permanent changes. No nutritional disease nor any obvious ill health is required. Changes have been found in the brains of adult rats whose only nutritional handicap has been to be suckled in larger-than-normal families during the brain growth spurt. They are fed a highly nutritious diet ad libitum from weaning at three weeks of age until they reach maturity. The permanent residual physical effects in adults of such mild growth retardation, when looked for in previously underfed adults, represent both deficits of and distortions from the normal, and include the following:

(a) Small brain size

This is a true microcephaly, the brain being permanently smaller than is appropriate for the body weight, in spite of having shown the traditional characteristics of "brain sparing" during the growth period (*17*). The brain is not uniformly small, being more so in the cerebellum than elsewhere. For both reasons, therefore, the small brain is distorted rather than merely deficient.

(b) Fewer cells

When measured by DNA analysis these smaller brains have fewer cells (*17*). There are disproportionately fewer in the cerebellum, and among the cerebellar neurons the later-dividing granular neurons are disproportionately reduced. There are also indications that some cerebral neurons are also disproportionately reduced (*16*). Most of the total cell deficit is probably glial, however. Here again there is distortion of brain structure in addition to simple deficiency.

(c) Less lipid

Many of the brain lipids are permanently reduced to a greater extent than would be predicted from the smaller brain size. Such deficiencies per unit fresh weight are selectively found in those lipids most characteristic of myelin (*12*), and this is a further example of distortion.

(d) Altered enzyme activity

Assessments of enzyme activities are bedeviled by argument about their significance and the significance of the various ways of expressing them. Should activity be expressed per cell (DNA), per unit protein, per unit fresh weight, per brain region, or how? The conceptual difficulties are greatly magnified in a tissue whose architecture and cell type are as heterogeneous as are those of the brain compared, for example, to the more homogeneous liver. Such differences as have been found in the present context probably represent structural changes. For example, the activity of acetylcholinesterase per unit fresh weight in previously undernourished adult rats is much higher than in controls (*2*), in spite of having been lower during the early period of restriction (*1*). It seems very likely that the enzyme is related to structures (perhaps cholinergic nerve endings) whose concentration has been increased as a result of a differentially greater deficit of other structures. Interpretation can be extremely tortuous, but at least here is another distortion.

In summary, the evidence for the vulnerability of the brain growth spurt is very good. Certainly, however, it could never be claimed that it was the only vulnerable period of brain growth, even in the present restricted sense, without a much more careful analysis of the vulnerability of other stages, especially the earlier and quantitatively smaller phase of neuronal multiplication corresponding to the human second trimester. Nevertheless, the hypothesis remains a useful one and in general terms is well supported by the evidence.

Brain Growth Opportunity

It has recently been shown that the brain growth spurt is obliged to occur at a predetermined chronologic age, even when conditions are unfavorable and growth has been nutritionally retarded (*17*). The effect of such "retardation" is to reduce the extent of brain growth processes, not to delay their occurrence. This has been demonstrated by constructing reliable velocity curves of the accumulation of fresh weight, DNA, and cholesterol (a major brain lipid) in undernourished animals and normal controls. The smaller area under the velocity curves of the undernourished animals, together with their failure to exhibit "catch up" on restoration to a normal diet, accounts for the ultimate deficit. An example of this is illustrated in Figure 1 for the phase of (glial) cell division.

This introduces a principle of possibly great practical importance to human babies. If there is a once-only opportunity to grow the brain properly, it is presumably important that the best conditions should be provided at this time. There may even be something to be said for directing nutritional aid toward the relevant age-group in times of severe shortage at the expense of older individuals whose brain growth spurt is over.

The Extrapolation of the Vulnerable-Period Hypothesis to Man

It has been shown that the changes described in previously growth-retarded adult animals are related to the timing of the restriction to coincide with the period of the brain growth spurt. Leaving aside any consideration of whether such changes matter, it ought to be possible to predict which human babies are at risk in this sense. All that is required is to identify the human brain growth spurt, and this is under way.

A study of nearly 200 complete human brains reveals the following relevant facts:

(1) Human neuronal multiplication occurs mainly in the second trimester of gestation (*15*). The subsequent growth of dendrites and the establishment of synaptic connections is, by inference, later. Probably it occupies the remainder of the growth spurt.

(2) Thus the period corresponding to the vulnerable one discussed above in animals probably begins with the third trimester.

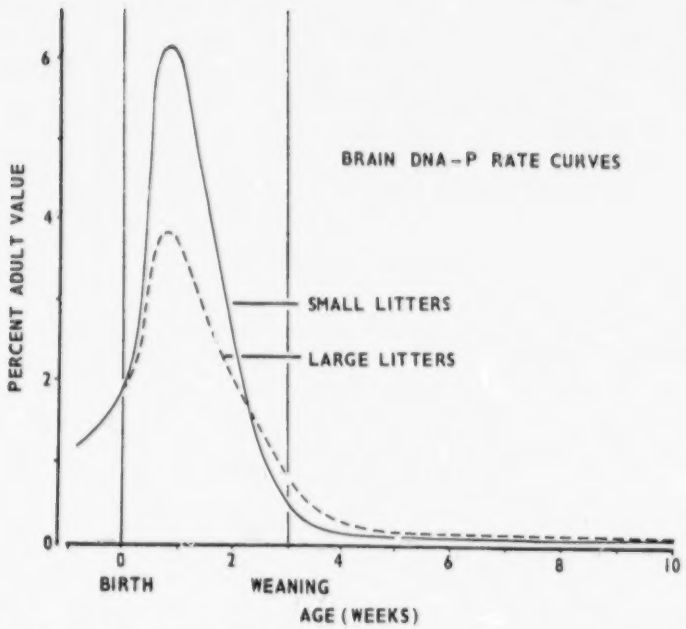

Figure 1. Velocity curves of DNA increment in the brains of rats suckled in small and large litters during the brain growth spurt. Growth retardation has not delayed the timing of the peak velocity (17).

(3) The end of the (glial) cell multiplication phase is at about 18 postnatal months (*13*), and the whole growth spurt is virtually over by two postnatal years (*13*).

Thus it can be seen that only about one-eighth of the human vulnerable period is fetal in term babies, a situation much closer to that of the infant rat than has hitherto been recognized. In this light, the eventual outcome of restricting human fetal growth would largely depend on the following theoretical consideration: Is good catch-up growth being instituted from birth onwards, and is there successful growth promotion during the last seven-eighths of the brain growth spurt that is postnatal in humans? How much recovery of physical brain growth is possible if good bodily growth is instituted after restriction occupying only the first one-eighth of the vulnerable period? The chances are that recovery would be virtually complete. This would convert the first two years of postnatal life from a period of vulnerability to an important one of opportunity. There is some evidence from experimental animal undernutrition that if rehabilitation is instituted well before the end of the brain growth spurt, there is apparent recovery (*24*). Recovery here was measured in terms of whole brain amounts, however, and it is not yet clear whether there are persisting regional deficits. It could be that restriction on early growth processes in those regions of the brain that develop early may produce lasting regional deficits which would be masked by analysis of whole brain. The matter is open to experiment.

It is therefore likely that any baby whose proper, lean-body-mass growth is seriously retarded for the whole, or for a substantial proportion of the period from 30 weeks' gestation to two full years of postnatal age may emerge with changes in the physical state of its brain comparable with those outlined above in rats.

Whether these will matter is an entirely open question, since it is completely unknown which parts of the physical brain are related to "higher mental function." It is also not known how much compensation may be available in the multiplicity of other developmental, environmental factors bearing upon the ultimate outcome. The most that can be suggested in practical, management terms is that, among all the other steps taken to promote baby welfare, the best true growth of babies should be ensured at this particular period. This applies equally to the baby in an underprivileged developing community, to the prematurely born, the "small-for-dates," and the normal term baby.

Finally it may be worth recording a personal note. In my view serious errors of thought are currently arising from a failure, mainly of pediatricians, to consider this subject biologically. It is nonsense to talk of the "fetal brain" or "neonatal brain" without taking into account the growth characteristics of the brain in the particular species under discussion. There is no demonstrable difference in principle between the human brain during the first one-eighth of its growth spurt (which is fetal) and the rat brain at the same developmental stage, just because in this species it is postnatal. Similarly, in considering the relevance to man of findings in animals, it is a travesty to ignore the three fundamentals of all studies of developmental undernutrition: its degree, its duration, and particularly its timing in relation to the whole developmental program. It seems to be unpalatable to some that man can often resemble rats or pigs very closely. Valid extrapolations *are* possible, but they must be very carefully made on a sound basis of knowledge of comparative development. This is especially so for those who would use subhuman primates. It is a fatally erroneous assumption that monkey brain development so closely resembles that of man, particularly in its timing, that such niceties of extrapolation can be ignored.

The lasting effects of early undernutrition on the structural development of the brain have necessarily been investigated in animals. The question may now be asked whether there are any behavioral consequences in those animals whose brains have been permanently altered? And can the animal model be used to help answer the all-important question whether humans suffer any lasting intellectual deficit following early growth retardation? There are some formidable difficulties in extrapolating from one species' behavior to another's, even though their patterns of physical brain growth are so similar. The suggestion that the human problem, inextricably entangled as it is with a multitude of socioeconomic and other particularly human factors, can be elucidated through animal studies in simple laboratory situations is probably realistic. A discussion of the often conflicting evidence from relevant experiments in animal behavior will be found elsewhere (*19*).

Summary

The evidence for the lasting structural changes in the brain related to the timing of early undernutrition is clear-cut. The brain growth spurt is by far the most vulnerable period in crude terms of quantitative ultimate achievement and measurable physical distortion. There is some evidence even from studies of human growth and development in privileged communities that seems to resemble the physical findings in animals (6), and some of the as-yet-scanty behavioral data from poor countries do support the idea that children can be permanently affected by malnutrition in their early years. Indeed, the correspondence is close between the vulnerable period for human behavioral development and the human brain growth spurt. It must be remembered, however, that in all developmental findings such correspondence can as easily be coincidental as meaningful.

It would not be stretching the evidence too far to say that in the light of present knowledge there is a period of human development ex-

tending from the second trimester of gestation well into the second postnatal year, during which the brain appears to have a once-only opportunity to grow properly. It is at this time especially important that children should grow at a proper rate and under the best environmental conditions. Among these nutrition is central to proper growth, a restriction of which may well have lasting behavioral consequences.

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SOME SPECULATIONS ON MECHANISMS INVOLVED IN THE EFFECTS OF UNDERNUTRITION ON CELLULAR GROWTH

Myron Winick, J. A. Brasel, and Pedro Rosso[1]

During the past 10 years a great deal of quantitative data has been accumulated on the normal cellular growth of various organs, regions of organs, and in some cases discrete areas. Growth has been viewed as a smooth progression from pure proliferation through combined hyperplasia and hypertrophy and finally to hypertrophy alone. Malnutrition has been shown to retard the rate of cell division during proliferative growth without changing the time at which proliferation ceases. Thus the resultant organ is smaller and contains fewer cells. This change is permanent. In contrast, the same degree of undernutrition during hypertrophic growth will inhibit the normal increase in cell size. This change, however, is reversible with rehabilitation.

It becomes evident in focusing on the developing brain that permanent cellular changes, if they are to occur, must come about as a consequence of early malnutrition. In the rat, cell division is over in brain by 21 days of age and only before that age will malnutrition induce a reduction in brain cell number. Various brain regions have individual patterns of cell growth. The most rapid rate of cell division in rat brain is in cerebellum and this continues to 17 days of life. In cerebrum, cell division is slower but continues longer, whereas in brain stem proliferation it continues at a very slow rate only until the 14th day of life. In cerebellum both neurons and glia continue to divide postnatally, whereas in cerebrum only glia divide at this time of life.

Neonatal malnutrition retards the rate of cell division in all areas studied. The earliest and severest effects are on those areas where cell division is most rapid. For example, a significant decrease in cerebellar cell number is noted after eight days of malnutrition beginning at birth. Changes in cerebrum occur later and are less severe, and there are only very few changes in brain stem. This reduction in the rate of cell division affects any cell type undergoing proliferative growth. In addition, the migration of cells from under the lateral ventricle to the hippocampus, which usually occurs on the 15th day of life, is curtailed—probably because the rate of cell division under the lateral ventricle is reduced—resulting in fewer cells able to migrate.

During the past few years these principles have been partially confirmed in man. Cell division normally ceases in human brain around the end of the first year of life. Proliferation in all three regions so far studied (cerebrum, cerebellum, and brain stem) stops at the same time. Malnutrition during the first year of life will reduce the rate of cell division and result in fewer cells in whole brain and in all three brain regions.

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There may be questions about the magnitude of this reduction, about the types of cells involved, and about the severity of the malnutrition necessary to produce an effect. There are certainly questions about the meaning of these changes, but the fundamental principle that undernutrition during proliferative growth will retard the rate of cell division in human brain appears well established.

How then does malnutrition exert its effect on cell division? During the past few years a number of laboratories have begun to address themselves to this problem.

During cellular growth and cell division we know that amino acids from the general body pool are supplied directly for protein synthesis and for the synthesis of nucleotides, which then enter the general body of nucleotide pool. The nucleotides are then used for either DNA or RNA synthesis. Newly-formed DNA is quite stable, whereas the newly formed RNA turns over and the rate of synthesis is in equilibrium with the rate of degradation. A number of enzymes are involved in all these processes and their activity depends, in part at least, on the quantitative and qualitative nature of protein synthesis. Thus the availability of amino acids will affect both nucleic acid and protein synthesis, and the amount and quality of the protein synthesized will in turn affect the synthesis of nucleic acids. To further complete the cycle, since RNA is an essential element in protein synthesis, changes in the quantity and quality of RNA will also affect the quantity and quality of the protein synthesized.

Where in this cycle does protein-calorie malnutrition exert its effect? Although the data are not yet complete, they certainly point to the fact that limitation of protein in the diet will decrease the availability of amino acids for protein synthesis. The work of Munro and more recently that of Miller has demonstrated reduced protein synthesis both in vivo and in vitro when either protein or amino acids in the diet are limited. Further, Munro has suggested that although any amino acid may be limiting experimentally, tryptophan appears to be the limiting amino acid in most physiologic situations. Thus, although definitive proof awaits measurement of amino acid pool size and tracking of amino acid pathways under conditions of protein-calorie malnutrition, present evidence strongly indicates that the amino acid pool size is reduced.

How is this reduced quantity of amino acid distributed? Amino acids for building blocks of protein are less available, as shown by the decreased incorporation of labeled amino acids into total protein. In contrast, there is some evidence indicating that amino acids are preferentially converted to nucleotides. For example, total nucleotide pool size in brains of neonatally malnourished animals is unaffected. Incorporation of labeled orotic acid into the nucleotide pool is significantly increased, however, and preliminary data suggest that incorporation of labeled amino acids into the nucleotide pool is also increased. We may postulate then that the synthesis of nucleotides is increased in brains of neonatally malnourished rats. If the nucleotide pool size does not change in brain or actually decreases in liver, where are these nucleotides being distributed? Incorporation of labeled nucleotides into DNA is markedly reduced in the brains of malnourished animals, demonstrating that there is a decreased distribution into DNA synthesis. In contrast, incorporation of labeled precursor into RNA is markedly increased in brains of neonatally malnourished animals. Thus the rate of DNA synthesis is reduced, whereas the rate of RNA synthesis is increased in neonatal protein-calorie restriction. One effect, then, of early malnutrition is a redistribution of available nucleotides. How is this redistribution controlled? What are the mechanisms involved in the decreased DNA synthesis, and how can we explain an increase in RNA synthesis in the face of descriptive data that conclusively demonstrate a reduced RNA content per cell?

We can answer the second question by examining the rate of RNA degradation after early malnutrition. There is a marked increase in the rate of decay of previously labeled RNA in liver of malnourished rats, and in brain there is a drop in the RNA/DNA ratio at a time when RNA synthesis is increased. Thus although the rate of RNA synthesis is increased, the rate of degradation must also be increased. The latter increase is presumably greater than the former, resulting in a net loss of RNA, which explains the drop in the RNA/DNA ratio or RNA content per cell.

At this point, we may summarize the effects of early malnutrition on some of the synthetic and degradative pathways involved in cellular growth. Incorporation of amino acids into total protein is reduced as is net protein synthesis. Incorporation of labeled precursors into the nucleotide pool is increased in the face of an unchanging or dropping total nucleotide pool size. Incorporation of nucleotides into DNA is decreased as is net DNA synthesis. Incorporation of nucleotides into RNA is increased, indicating an increased rate of RNA synthesis in the face of a decrease in cellular RNA content. The rate of RNA degradation is markedly increased.

In an attempt to explore some of the mechanisms by which these dynamic changes occur, the activity of certain of the enzymes involved in the regulation of the steps just described has been measured. DNA polymerase is an enzyme involved in the terminal phase of DNA synthesis. In a number of nonphysiologic situations, activity of this enzyme has been shown to increase under conditions that stimulate DNA synthesis. Moreover, the increase has been shown to precede the increase in DNA synthesis. Recent experiments in our laboratory have demonstrated that the response to unilateral nephrectomy in the opposite kidney is hyperplastic in infant rats and hypertrophic in adult rats. This hyperplastic response is preceded by a burst of DNA polymerase activity in the remaining kidney of the infant animal, whereas the polymerase response in the adult is much less.

More recently it has been shown that activity of this enzyme in liver of growing rats is in part under the control of pituitary growth hormone. Hypophysectomy reduces enzyme activity and growth hormone replacement elevates the activity before any increase in DNA synthesis can be shown.

We have demonstrated in brain that the activity of DNA polymerase parallels the rate of cell division during normal growth, and that this parallel relationship holds when various brain regions are studied. Our data show that the activity of this enzyme is an excellent indicator of the rate of cell division and suggest that during normal growth DNA polymerase may play a role in regulating the rate of DNA synthesis. We believe that neonatal malnutrition will reduce the activity of this enzyme in rat liver.

Thus, the evidence at this stage indicates that one way by which early malnutrition may curtail the rate of DNA synthesis and perhaps indirectly regulate the distribution of available nucleotides is by reducing the activity of DNA polymerase.

While we have not investigated the enzymes involved in RNA synthesis, others have begun such investigations. For example, Metcoff and coworkers have demonstrated an increase in RNA polymerase activity in leukocytes of undernourished children and in placentas from mothers who were malnourished and whose infants demonstrated intrauterine growth failure. Indicative as these data may be, experiments are lacking that reveal an elevation in the activity of RNA polymerase in tissues exposed to neonatal malnutrition and correlate this increased activity with an increase in the rate of RNA synthesis.

The degradative phase of RNA metabolism is of particular interest since it is the increased rate of degradation that accounts for the net loss of RNA per cell. The enzyme alkaline RNase has been presumed to be involved in RNA

catabolism. Available data indicate that under most circumstances activity of this enzyme is inversely related to cellular RNA content. We have, therefore, undertaken a series of investigations designed to explore the role of this enzyme during normal growth and the alterations that may occur in early malnutrition.

During normal brain development the activity of this enzyme per cell increases, but this increase is exactly proportional to the increase in cellular RNA content and the relationship between enzyme and substrate remains constant throughout development. Total activity of alkaline RNase increases per milligram of DNA per cell throughout development except for a drop at birth and again at 17 days of age. By contrast, specific activity per milligram of protein declines during development. When activity is expressed per milligram of RNA per milligram of substrate, there is no change during development. These data emphasize the importance of enzyme activity's mode of expression and point out clearly that interpretation of changes in such activity may depend a great deal on the reference point employed. By using these three reference points, a clearer picture can be drawn. Activity per cell increases during brain development; this increase is less than the increase in other cellular proteins and hence the specific activity drops. The increased activity per cell, however, is directly proportional to the increase in RNA content per cell that occurs during development, and therefor the activity per milligram of RNA does not change. This constant relationship between RNase activity and RNA content under circumstances in which both are changing again indicates a role for this enzyme in the regulation of RNA metabolism. In the studies noted above, only total cellular alkaline RNase activity was examined because of our initial findings of very small amounts of activity in the nuclear fraction and the absence of free activity (non-inhibitor-bound) in the cytoplasmic fraction.

In other tissues, however, alkaline RNase is active intranuclearly as well as in the cytoplasm, and is present as both bound and free enzyme. Our own preliminary laboratory data indicate that the nuclear activity is in some manner related to the rate of RNA synthesis within the nucleus, whereas the cytoplasmic enzyme is involved in the regulation of RNA catabolism in the cytoplasm. For example, if one examines the activity of cytoplasmic RNase in three different adult tissues that catabolize RNA at three different rates, a direct correlation between enzyme activity and rate of catabolism is immediately apparent. The most rapid rate of RNA degradation occurs in kidney, with liver and brain following in descending order. The highest activity of RNase per cell also occurs in kidney, with liver and brain, respectively, following. Moreover, the differences in enzyme activity are directly proportional to the differences in catabolic rate.

These data have convinced us that alkaline RNase must play a role in the regulation of RNA metabolism and, indirectly, protein synthesis by influencing the rate of RNA catabolism. We have accordingly studied the effect of such malnutrition on the activity of alkaline RNase since, as previously pointed out, RNA catabolism is increased in brains of animals exposed to early malnutrition. Malnutrition imposed at birth will elevate the activity of this enzyme in rat brain, and this elevation progressively increases as the duration of malnutrition increases. Although these data are expressed per milligram of DNA per cell, the same findings are present if the data are expressed per milligram of protein or per milligram of RNA. Neonatal malnutrition thus selectively elevates the activity of this enzyme in the face of a decrease in both overall protein synthesis and a fall in tissue RNA content.

At this point we can summarize what is known about the effects of early malnutrition on cellular growth of the brain and present our hypothesis of the effects of malnutrition

on the regulatory mechanisms involved in the control of cellular growth. Malnutrition during proliferative growth will curtail net protein, RNA, and DNA synthesis and result in an organ with a reduced number of cells. It would appear that any cell type in any region where cells are dividing is vulnerable to the effects of nutritional deprivation. Early malnutrition limits the availability of amino acids for incorporation into protein, thereby reducing the rate of protein synthesis. In contrast, an increased flow of amino acids enters the nucleotide pool, which presumably limits even further the availability of these amino acids for protein synthesis. Nucleotides are removed from the pool much more slowly along the pathway to DNA synthesis, since the synthesis of DNA is occurring at a much slower rate than normal.

This reduced rate of DNA synthesis is at least in part a consequence of the reduced activity of certain enzymes involved in that synthesis, for example, DNA polymerase. In contrast, nucleotides are removed much more quickly along the pathway to RNA synthesis, since synthesis of RNA is more rapid than normal. This results in either a depletion in the size of the nucleotide pool, as occurs in liver, or a maintenance of normal amounts, as occurs in brain. Regardless of the effect on pool size, however, the distribution from the pool has been altered by early undernutrition. The increase in RNA synthesis may direct alterations in protein synthesis that result in selective elevations in certain proteins, for example, RNA polymerase and alkaline RNase. The increased RNA polymerase activity may further stimulate the enhanced RNA synthesis, whereas the increased activity of alkaline RNase may initiate the increased rate of RNA degradation that has been demonstrated. This increased catabolic phase may in turn be responsible for the shift in polysome pattern described by Munro, and through this mechanism may contribute even further to the selective reduction in protein synthesis.

In addition to the opening of new areas of research aimed at further exploring the mechanisms by which early malnutrition exerts its effects on cellular growth, the data just reviewed have opened two avenues of research for reexamination. The entire problem of prenatal malnutrition can be reexamined using these more sensitive markers of tissue nutritional status. This approach seems warranted, especially in view of the less marked quantitative changes in weight, and protein, RNA, and DNA content that have been reported in certain kinds of intrauterine malnutrition. Second, some of these tissue changes themselves and the reflection of these changes in body fluids could provide a clinically sensitive index of nutritional status and recovery from malnutrition.

Let us address ourselves to the first problem, "intrauterine malnutrition." If one examines all the available data from all species of experimental animals studied, it becomes quite clear that at least two types of intrauterine malnutrition exist. One type produces obvious changes in cellular growth of the fetal brain, whereas the other produces little if any change in fetal brain when measurements of weight, and protein, RNA, and DNA content are used.

As we shall see, however, more subtle changes as measured by some of the parameters just described do occur. These two types of fetal malnutrition do not, as far as we can tell at present, depend on the species employed but rather on the method by which the malnutrition is induced. For example, "placental insufficiency" will result in retarded fetal growth. This condition has been produced by ligating the uterine artery in rats and more recently by ablating a portion of the placenta in monkeys. In the rat such a ligation produces a reduction in weight, and protein, RNA, and DNA content in placenta and most fetal tissues. Brain, however, is unaffected. These data have been substantiated by Minkowski and colleagues, and more recently by Oh. A similar situation apparently

occurs in the monkey following ablation of a portion of the placenta. Cheek and coworkers have demonstrated, using such a model, that although profound fetal growth failure will occur, brain weight and protein and DNA content are unaffected, and RNA content is reduced only about 5 per cent in cerebellum. This relatively small reduction may become more significant when considered together with more recent data about other tissue parameters. Thus, both in the rat and in the monkey this type of placental insufficiency results in a markedly disproportionate type of growth failure in which brain is relatively spared and organs such as liver markedly affected.

If we now reexamine this model using our "newer markers" of tissue nutritional status, certain changes not previously seen become obvious. Within 24 hours after ligation a marked elevation of placental RNase activity can be demonstrated. Enzyme activity increases in inverse proportion to the distance from the ligation. There is a marked elevation in the proximal placenta, a milder elevation in intermediately located placentas, and minimal changes in those located distally. If we limit our observations to the proximal placenta, alkaline RNase activity becomes elevated within 24 hours and remains elevated for at least 96 hours. This increase in activity precedes any changes in placental weight, or protein, DNA, or RNA content. In the fetal organs, there is a marked increase in liver RNase within 24 hours, with brain unaffected. By 48 hours, however, both brain and liver RNase are distinctly elevated. Thus, by examining activity of alkaline RNase, changes in brain can be demonstrated after 48 hours of ligation in the absence of any reduction in weight, or protein, DNA, or RNA content.

These data become even more interesting when coupled with the observations of Cheek and coworkers in the monkey. Although those investigators did not measure alkaline RNase activity, their results demonstrating a slight reduction in cerebellar RNA content may be more meaningful in this context. At present, then, the available data indicate that this type of placental insufficiency will produce certain changes in RNA metabolism of fetal brain without permanently affecting cellular growth as measured by brain weight, protein, or nucleic acid content. What the significance, if any, of this increased enzyme activity is remains to be determined.

In contrast to the placental insufficiency model, maternal protein restriction in rats, pigs, and guinea pigs produces a symmetrical reduction in weight, and protein, RNA, and DNA content of all organs including brain. Brain is affected by the 16th day of gestation, and all areas examined, including white and gray matter, demonstrate a marked reduction in the number of dividing cells. By birth there is an approximately 15 per cent reduction in cell number when this model is used. This reduction agrees with the findings of Zamenhof and colleagues, and is roughly of similar magnitude to the reduction in cell number found in the other fetal organs. Thus this type of fetal malnutrition is quite different from the placental insufficiency type. Here we see symmetrical growth retardation in which the brain is not spared. Combining maternal restriction with postnatal restriction, we can produce even more marked effects on cellular growth of the developing brain. Although in either prenatal or postnatal malnutrition there is an approximately 15 per cent reduction in brain cell number, the combination of both produces a 60 per cent reduction.

If we now turn to measurement of our more recently described markers of tissue nutritional status, we can demonstrate first that activity of DNA polymerase parallels the rate of cell division during normal placental growth and that this type of maternal malnutrition will result in reduced activity of this enzyme in placenta by 12 days of gestation. Moreover, alkaline RNase activity is markedly elevated in

such placentas. Changes in other fetal organs including brain are currently being investigated. Activity of both DNA polymerase and alkaline RNase has thus proved a sensitive index of nutritional status—at least in placenta—in rats exposed to maternal protein restriction.

How can these changes provide us with clinically useful tools for the assessment of nutritional status? DNA polymerase activity has recently been measured in human leukocytes and has been shown to increase markedly in situations of abnormally rapid cell division such as leukemia. This increased activity moreover precedes by several days any increase in leukocyte cell number and has been used to predict recurrence of disease after drug-induced remission. The possibility exists that enzyme activity may be reduced in leukocytes of malnourished children and that activity might increase with therapy. We intend to explore this possibility. In addition, since it has been shown that DNA polymerase activity parallels the rate of cell division in tissues other than brain, activity in a muscle biopsy could give us a quantitative measure of the rate of cell division in muscle of malnourished children. This is only speculation, but we intend to investigate the possibility. Finally, since activity of this enzyme is reduced in placenta in experimental malnutrition, we intend to measure its activity in placentas of malnourished women. To this end we have worked out the requirements and measured activity in normal human placenta.

As previously mentioned, Metcoff and coworkers are actively examining leukocytes and placenta for RNA polymerase activity in populations of malnourished women. We may hope their investigations will also sharpen our ools for assessing nutritional status.

We have recently focused our attention on alkaline RNase as a clinically useful marker of nutritional status. Examination of placentas of a group of malnourished mothers in Quito, Ecuador, reveals an elevated RNase activity when they are compared to placentas from normally nourished women in the same city. This enzyme is present not only in all tissues but in normal plasma and urine, and we have measured it in normal amniotic fluid. Obviously changes in the activity of this enzyme in any of these fluids would provide a practical approach to the monitoring of either postnatal or prenatal nutritional status. Plasma RNase exists almost entirely in the free form, and during development the activity of this enzyme per milliliter of plasma decreases. There was a significant increase in enzyme activity in plasma from 14 malnourished children when compared to that from age-matched controls. Moreover, plasma activity returned to normal in all cases after only two weeks of therapy. Sometimes this return to normal preceded any noticeable weight gain in these children. By contrast, activity of alkaline RNase in the urine of marasmic children is reduced, indicating a reduced clearance of the enzyme. Therefore, when the urine and plasma data are combined and expressed as a u/p ratio, the most marked changes are noted. These data demonstrate that the activity of alkaline RNase in plasma and urine of marasmic infants is a sensitive index of nutritional status. The data have encouraged us to investigate this enzyme in less severe malnutrition and in amniotic fluid during prenatal undernutrition, both in our animal models and in human populations.

In an attempt to uncover other useful biochemical indices of fetal growth by monitoring changes in amniotic fluid, we have examined the concentrations of urea in one of our animal models and nondialyzable hydroxyproline in the human.

It has been shown that urea excretion can be used as a rough measure of the rate of protein synthesis and degradation. Studies in Jamaica and Africa have indicated that urea excretion in severely malnourished children is reduced. Since amniotic fluid is composed largely of fetal urine, we have studied urea concentration in rat amniotic fluid during nor-

mal development and after uterine artery ligation. The data indicate an increase in urea concentration during normal development and a marked reduction following uterine artery clamping in fetuses showing 25 per cent or greater reduction in body weight. Although these data are still in the early stages of collection, we intend to pursue these findings both in rats and in the human.

Urinary hydroxyproline has been shown to be elevated under conditions of rapid collagen synthesis. More recently it has been demonstrated that under these conditions, it is the large molecular weight nondialyzable fraction (LMN Hypro) that increases. We have measured LMN Hypro concentration and content in human amniotic fluid at various stages of pregnancy. We have found that the concentration of LMN Hypro remains relatively constant during the first 28 weeks of gestation and then decreases. This drop in concentration is not due to any dilutional effect, since amniotic fluid volume increases more slowly and in some cases even decreases toward the end of pregnancy. At present the best working hypothesis seems to be that at around 28 weeks fetal swallowing occurs, LMN Hypro is degraded, and smaller peptides are either utilized or reexcreted. The smaller peptides then pass into the maternal circulation and are excreted in maternal urine. We have recently been able to document an increase in total hydroxyproline in maternal urine during the last trimester. We are now planning to fractionate the urine and see if it is a small polypeptide molecule that increases. Again, although only in the early stages of investigation, determination of LMN Hypro in amniotic fluid might provide a means for monitoring early fetal growth, and determination of small hydroxyproline polypeptides in maternal urine during the last trimester might be a way to monitor late fetal growth.

Finally, the previously described evidence in animals shows that maternal protein restriction will affect fetal growth and brain development. Data in man are less clear and mostly indirect. The available data do, however, indicate that this may occur. For example, examination of brains of children who died of malnutrition reveals three distinct groups. Children who died of kwashiorkor after 18 months of age had normal brain DNA contents, the protein/DNA ratio being reduced. By contrast, children who died of marasmus during the first year of life could be divided into two groups. In the first there was a 15 per cent reduction in cell number, but in the second the reduction was 60 per cent. The difference between these groups was that in the former all the infants weighed more than 2,500 g at birth while in the latter they were all below 2,000 g at birth. These data indicate that either they were true prematures and the premature infant is more susceptible to postnatal malnutrition, or that they were infants who were already malnourished in utero and represent the clinical counterpart of the doubly deprived rat previously described. More recently Chase has reported reduced DNA content in brains of infants who were "fetally malnourished" and who died shortly after birth. Although the data are extremely limited, we must continue to investigate the possibility that fetal malnutrition may affect brain growth in the human. To this end the techniques described above for monitoring human fetal growth may prove exceedingly useful.

In summary, during the past five or six years a number of descriptive observations on growth of various organs have been made using measurements of weight, and protein, RNA, and DNA content. In rat brain, using these measurements, it has been shown that early malnutrition will retard the rate of cell division in any region undergoing proliferative growth and result in a permanent deficit in cell number. Any cell type dividing will be affected. In the human, a few studies have led to similar findings. More recently, experiments have been

undertaken that are designed to explore the mechanisms by which these changes in cellular growth occur. These studies, while still in progress, have already revealed that certain alterations in protein synthesis, distribution of amino acids and nucleotides, RNA synthesis, RNA degradation, and DNA synthesis take place. The activity of enzymes controlling these processes is also altered. Specifically, DNA polymerase activity is reduced and alkaline RNase activity elevated. These tissue changes produced by malnutrition have allowed us to explore more deeply the effect of other types of nutritional deprivation. Two distinct types of fetal malnutrition can be described. One is a placental insufficiency that produces only subtle changes in RNA metabolism in the fetal brain, as demonstrated by a delayed increase in alkaline RNase activity, and the other is due to maternal protein deficiency that produces all the changes in fetal brain described with postnatal malnutrition.

These tissue changes have also supplied clinical markers for determining nutritional status and response to therapy. Alkaline RNase is thus elevated in placentas of undernourished women and in serum of undernourished children. Moreover, it is decreased in urine of these children, causing a marked reduction in the u/p ratio. With therapy it rapidly returns to normal.

Urea and LMN Hypro concentration in amniotic fluid and smaller peptide hydroxyproline concentration in maternal urine are also being investigated as possible markers for fetal growth and nutritional status.

The problems we must yet solve are enormous. Do the changes described here have any functional significance? Does prenatal malnutrition in the human affect the fetal brain? If so, what kind of malnutrition? How are these effects manifested? What are their significance? Perhaps we do not yet have the means to answer these questions, but the data presented at least demonstrate that we are sharpening our tools, refining our measurements, and applying the new findings to some of these perplexing problems.

SMALL-FOR-DATES OFFSPRING: AN ANIMAL MODEL

R. J. C. Stewart[1]

It is generally accepted that the earlier in postnatal life a dietary deficiency can be established, the more severe are its effects. This is particularly true with respect to protein-calorie deficiency and it seemed probable that a prenatal deficiency might produce very severe changes.

Intrauterine malnutrition was produced in dogs whose mothers were fed a protein-deficient diet (NDpCal% = 6.8) from weaning (*12*). The dietary regimen caused no changes in gestation times, no difficulties in parturition, and no significant increase in the number of stillborn, but mean birth weights were 20 per cent lower than those of controls. This was not, however, a consistent reduction, some animals weighing as much as the heaviest controls (> 350 g) and others being markedly small-for-dates (SFD) and weighing as little as 140 g. When the congenitally malnourished pups were suckled by their own mothers, there was a high death rate (41 per cent) during suckling; after weaning they grew less rapidly than normal pups, irrespective of the quality of their diet (Figure 2, (*12*)). Those given diets of low protein value (NDpCal% = 5.0) developed some incoordination, a proportion showed athetoid movements of the head and limbs, and some suffered severe and repeated convulsive seizures.

The congenitally malnourished dogs exhibited alterations in the electrical activity of their brains (*9*), modifications of their carbohydrate metabolism (*7*), and changes in the weight and histologic appearance of the central nervous system, endocrine glands, bones, and many other tissues (*11*). Animals allowed to reach adulthood could always be differentiated from well-fed controls by their short legs, unusual behavior, and tendency to obesity.

It was clearly important to determine whether members of a colony that had been maintained for several generations on the deficient regimen could adapt their metabolism and regain the original size, stabilize at a smaller body size, or progressively deteriorate. Owing to a shortage of accommodation the work could not be continued with dogs and, as it was known that restrictions in the quality (*3, 4, 5*) or quantity (*2*) of a rat's diet led to metabolic, physical, and behavioral alterations in her offspring, the tests were continued with rats.

From the results of the studies mentioned above and other work (*1, 13, 14, 16*) we concluded that a more severe dietary restriction would be necessary in rats than in dogs, and for the first experiment reduced the protein value of the rats' diet to NDpCal% = 5.0. In the first generation there was a large number of SFD offspring, the mean litter weight fell by 21 per cent ($p < 0.01$), and the animals grew less rapidly than the controls both before and

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after weaning (*15*). But there was a very high loss during suckling (63 per cent), many of the survivors failed to rear a litter, and the feeding of a powdered diet proved wasteful in both materials and labor.

Efforts were then directed to the production of diets with higher protein values (NDpCal% = 6.8 and 10.0) which could be "cubed" (*10*).

Colonies have now been maintained on cubed diets for eight generations. The reduction in the mean birth weights of the offspring of marginally malnourished mothers has been confirmed, but there is no statistical evidence of any change in the average values from generation to generation (Table 1). The number of young per litter has risen slightly in the well-fed and declined in the underfed colony, so that the average weight per litter is markedly different. Birth weights vary widely in both colonies—from 3.5 g to 7.0 g in the control and 2.8 g to 6.3 g in the deficient group—but in the latter colony 75 per cent of the seventh generation were born weighing less than 5.0 g. SFD offspring have been defined in these experiments as term rats that had birth weights more than 2 SD below the mean of the well-fed colony. The mean birth weight of pups from the control mothers was 5.6 g and those born at less than 4.5 g are considered SFD. The proportion of SFD varied between 2 per cent in the fourth and 4 per cent in the seventh generation, with a mean of 3 per cent for the whole colony. As the colonies were developed from litter mates, there are minimal "genetic or race differences," and the SFD criterion of less than 4.5 g in the normal group can also be used to define SFD in the malnourished colony. In the latter the proportion of such young is much higher, varying from 11 per cent in the third to 43 per cent in the seventh generation, with a mean of 28 per cent. Both before and after weaning the congenitally malnourished offspring grow and develop slowly, so that at four weeks of age the young have only 50 per cent of the weight of the age-matched controls. Hair growth is obviously affected, and at 10 days of age some pups are practically bald. On the other hand, eye opening does not appear to be delayed. Weight differences between the sexes appear later than expected, and in the latest (eighth) genration som delay in vaginal opening times is suspected (only a small number of animals are now available).

Table 1. Birth weights of rats maintained on diets of different protein values.

	Diet B NDpCal% = 10.0 Mean and SD g	Diet A NDpCal% = 6.8 Mean and SD g
Generation 0	5.6 ± 0.46	5.6 ± 0.46
Generation 1	5.3 ± 0.39	4.9 ± 0.56
Generation 2	5.5 ± 0.36	4.6 ± 0.45
Generation 3	5.4 ± 0.58	5.0 ± 0.48
Generation 4	5.6 ± 0.46	4.8 ± 0.65
Generation 5	5.6 ± 0.60	4.7 ± 0.60
Generation 6	5.6 ± 0.48	4.8 ± 0.60
Generation 7	5.5 ± 0.58	4.3 ± 0.75
Generations 0-7	5.57 ± 0.51	

Much of the slow growth in early life may be attributed to the poor mammary development of the mothers (see Plate 11, (*11*)), and a deficient supply of milk undoubtedly contributes to the high preweaning losses (45 per cent). Some of the losses are less easily explained. Occasionally what appear to be reasonably efficient mothers will scatter their nests around the cage, kill the young, and, although the walls and floor are spattered with blood, not eat them. Can this be an episode similar to the convulsive seizures observed in the dogs? Convulsive seizures have never been seen in these rats. Behavioral changes are restricted to a slightly enhanced activity with occasional tremors in early life, followed by a prolonged sluggish period during which the animal reacts more violently than normally to unexpected noise or mild electric shock.

Preweaning food restriction is not the only factor in poor growth. Animals of the fifth generation fostered at birth to normal mothers plateau at weights below those of the control

colony, although during early life they appear to grow normally.

It must be reiterated that, as with the dogs, the adequacy of the poor diet varies with the physiologic state of the recipient, being deficient during early growth, gestation, and lactation but adequate for adult maintenance. It is not surprising, therefore, that the very high percentage deficits observed in body weights at four weeks of age became proportionately less by six months (Table 2). The effects of protein-calorie deficiency on other values—body, head, and femur lengths—are also shown in Table 2. Of the organs weighed—liver, kidney, endocrine glands, and brain—the last was the least affected. Tables 3 and 4 show the weights of the whole and various parts at three and six months of age in both male and female rats. The differences between the colonies are small, but just as averages of the whole colony did not give a complete picture of birth weights, they do not reveal all the distributional changes in brain size. Brain weights varied between 1.47 g and 2.02 g in the control males but only 9 per cent were below 1.60 g, whereas in the deficient males, although the range was only slightly lower (1.36 g to 1.99 g), 46 per cent were below 1.60 g. A

Table 2. Measurements[a] of six-month-old rats from colonies maintained on diets of different protein values.

	Diet B NDpCal% = 10 Means and SD		Diet A NDpCal% = 6.8 Means and SD	
	♀	♂	♀	♂
Body weight (g)	270 ± 31.7	399 ± 72.6	191 ± 26.7	290 ± 35.5
Body length[b] (mm)	190 ± 7.0	213 ± 12.1	175 ± 7.0	187 ± 6.7
Head length (mm)	50.1 ± 1.9	52.9 ± 2.5	48.0 ± 2.3	50.1 ± 3.5
Femur length (mm)	34.7 ± 0.61	39.3 ± 0.63	31.7 ± 1.7	34.7 ± 1.5
Brain (mg)	1639 ± 159	1772 ± 178	1583 ± 153	1625 ± 128

[a] After formalin perfusion except for body weight.
[b] Excluding tail.

Table 3. Brain weights[a] of male rats from colonies maintained on diets of different protein values.

	Diet B NDpCal% = 10.0 Means and SD		Diet A NDpCal% = 6.8 Means and SD	
	3 months	6 months	3 months	6 months
Brain stem (mg)	163 ± 33	173 ± 21	127 ± 12	160 ± 27
Cerebellum (mg)	254 ± 28	270 ± 30	207 ± 25	238 ± 24
Forebrain (mg)	1285 ± 147	1323 ± 140	1124 ± 111	1229 ± 89
Whole brains (mg)	1720 ± 185	1772 ± 178	1459 ± 135	1625 ± 128

[a] After formalin perfusion.

Table 4. Brain weights[a] of female rats from colonies maintained on diets of different protein values.

	Diet B NDpCal% = 10.0 Means and SD		Diet A NDpCal% = 6.8 Means and SD	
	3 months	6 months	3 months	6 months
Brain stem (mg)	138 ± 20	162 ± 18	122 ± 21	157 ± 31
Cerebellum (mg)	229 ± 18	244 ± 23	195 ± 28	223 ± 23
Forebrain (mg)	1154 ± 126	1233 ± 127	1058 ± 123	1202 ± 110
Whole brains (mg)	1520 ± 159	1639 ± 159	1375 ± 163	1583 ± 153

[a] After formalin perfusion.

similar but less marked situation occurs in the slower growing females.

Clearly, many of these animals have brains and other organs that, while small for their genetic background, are not small relative to body size.

Is there any evidence that the changes described in the malnourished colony vary from generation to generation? Total litter weights are, and average birth weights may be declining. There is an increase in the number of very small individuals, and although no statistics are available, there is a firm impression among those handling the rats that a rat of generation 7 weighing 3 g has a better chance of survival than did one of similar weight in generation 1.

Table 5 attempts to summarize the available information. It will be seen that all the values listed are lower for the sixth-generation males than for the total male population. If confirmed, the alterations in brain weight in later generations will be of particular interest. The average weight in well-fed males at six months of age was 1.77 g and there was no difference in the first malnourished generations. After four generations of malnourishment, however, the weight fell to 1.66 g, in the fifth generation to 1.60 g, and in the sixth to 1.52 g. It must be emphasized, though, that the brains are still large relative to body weight (see percentages in Table 5). When the brains were divided (Tables 3 and 4), it became clear that the cerebellum was the most consistently and severely affected. This is in keeping with the histologic observations in rats aged one, three, and six months.

The granular and molecular layers of the cerebellum are reduced in size and the former in density. The Purkinje cells are poor in chromatin and there is an increased number of Bergmann cells. Areas of the forebrain and brain stem are also modified, there appears to be a reduced number of cells in the cerebral cortex, the Nissl granules are reduced in some motor nuclei, and there is an increased number

Table 5. Measurements of protein-calorie-deficient rats, expressed as percentages of normal values (6 months of age).

	Females	Males	
	Generations 1–6	Generations 1–6	6
Body weight	71	73	66
Body length	95	88	85
Head length	98	94	87
Femur length	91	88	84
Brain weight	97	92	86

of active neuroglial cells. Similar but more marked changes were seen in the brains of the 15- and 21-day-old offspring of mothers fed a low-protein diet during gestation (*8*). These animals also exhibited deficits in deoxyribonucleic acid and gangliosides, but the work of Winick and Noble (*17*) and Dobbing (*6*) shows that some of this change must be attributed to poor postnatal development. Preliminary tests (six brains only) indicate that in the newborn of the sixth generation of the malnourished colony there may be a reduction in the amount but an increase in the concentration of deoxyribonucleic acid.

The important and outstanding questions are whether or not the brains of adult animals show chemical changes that lead to the histologic modifications and if so, whether the modifications adversely affect behavior and learning? The simple answer is that we do not know. Tests, using animals of generations 8 and 9, are planned with Drs. Dickerson and Birch, and we hope these aspects will then become clear.

Our present experiments show that intrauterine or congenital malnutrition occurs in animal colonies reared on inadequate diets; that, after the first-generation, reductions in body weight continue but are small, and that there may be a later adjustment in brain weight. Even after six generations the brains, though small for genetic background, are large relative to body weight. While their quality may be suspect, there is no proof that they are abnormal.

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SUMMARY OF SESSION I

Herbert G. Birch[1]

We have listened to four extremely interesting papers. The speakers all agree that there are indeed changes in physical structure, in cell number, and in certain enzymatic characteristics when malnutrition occurs at particular points in the developmental course. They disagree about the specific age levels at which organisms may be most sensitive to the influence of malnutrition and about the ubiquity of the phenomena for all species of organisms.

When Dr. Cheek began his paper and presented a comparative view of mammalian subspecies, he sought to argue that nutritional insults at particular points of development are important for small mammals, less important for larger mammals, and probably still less important for subhuman primates and man. Though this was his thesis, he neither developed it with enough system to be convincing nor sufficiently analyzed explicit problems and issues that must be considered if any cross-species comparisons are ever validly to be made. One problem that must always be dealt with across species is the developmental rate that characterizes a species and, in consequence, the durations of insult that would be needed to produce equivalent insults. The second point that was not systematically considered is the degree to which the ages at which insults occur correspond in fact as homologous points in the developmental courses of the target organ—in this case, the brain. For example, one has great difficulty in comparing and defining equivalent developmental time points in precocial species such as the guinea pig as contrasted to altricial species such as the rat. Given gross differences in developmental calendars, it is essential in interspecies comparisons to define the equivalent time points for comparisons of effects.

Whether primates and particularly man are immune from the effects of malnutrition cannot be concluded from the data presented. The models used are limited and produce particular pieces of evidence that, though interesting to consider as special questions, do not contribute firm evidence that other methods of inducing fetal malnutrition would be ineffective in limiting growth and development, e.g., ligation versus maternal malnutrition. Though this finding opens up enormously important questions as to the types of change in maternal-fetal transport that result under these different conditions of interference, one clearly cannot accept the particular procedure of ligation as the experimental analogue of developmental inadequacy. These issues resulted in a considerable amount of parallel play among the various speakers as to whether their findings agreed with the particular picture that had been presented. No real agreement was apparent.

Another set of issues raised was about a point of method. There are indeed very good reasons for wanting to know what the specific break points in a developmental course are. For example, if one were dealing with the problems of prevention, one would be concerned with the particular points at which vulnerability existed in any individual's developmental course. All the speakers agreed that there are indeed such critical points in development. What they disagreed about is where those points are.

It was argued that we know that neuronal replication is completed in various organisms before the peak of glial replication occurs. As

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a consequence, one would hope that it would somehow be possible to define in development a number of kinds of points in time when neuronal replication is at its peak and other points in time when glial replication would occur. It would be delightful if these phenomena did not overlap. From the point of view of analyzing biologic systems, they unfortunately do. If these phenomena did not overlap, we would have alternating peaks and plateaus, and no one would be fighting about anything. What we have, in fact, is a pattern of glial replication proceeding at a relatively low rate and increasing in its replication rate in the later period, neuronal replication proceeding at a more rapid rate in the earlier period, and intermediate periods reflecting some kind of mix. The question then becomes, How can we sort out this kind of mix in relation to the problem?

Considerable discussion took place in which Dr. Dobbing gave evidence to support the hypotheses that have guided his work most productively for many years: permanent changes occur in brain because of nutritional restriction during appropriate periods of brain growth, and these changes in brain are not unique to brain itself since alteration of brain structure reflects general restriction of growth. He argued that no basic species differences exist if relevant time dimensions are considered, and that if one applies insults appropriately with respect to rates and course of development, common outcomes are to be anticipated in any species under consideration. He has further asked us to consider two different kinds of model. One may be viewed as a crisis model in which extremely severe insults are applied to organisms for very brief periods. This is contrasted to mild and chronic models of insults that may be applied over longer periods.

A number of variations of these models have been discussed, any of which could have different consequences for development. Mr. Stewart, for example, has used a quasigenetic, intergenerational chronic model to study the cumulative consequences of adaptation to marginally adequate nutritional inputs. Dr. Dobbing has described modest restrictions for periods in which particular features of growth are taking place. In some of his studies Dr. Winick was concerned with acute nutritional insult; in other studies, with insults similar to Dr. Dobbing's, and in still others at the human level in particular, with chronic conditions followed by acute, severe exacerbation. Whether all these conditions should result in identical outcomes is, in my opinion, dubious. I think that if we begin to examine these problems in terms of the actual conditions of insult—its timing, severity, and duration—we cannot treat all kinds of malnutrition as alike because the same word, "malnutrition," is used to describe a variety of conditions. We may indeed be able to define specific conditions that have particular consequences for the development of organism. Within this framework, then, it seems to me that Dr. Winick has turned our attention in one direction and Dr. Dobbing in another. Dr. Dobbing has suggested that the number of cells that are in brain may not be the critical factor in defining the functional integrity of the system. He and others have argued that such things as dendritic proliferation, normal branching, the development of synaptic organization, and the properties of firing in the brain all make particularly important contributions to integrated organization.

Lashley (*1*) and others showed that many functions may still be completely unimpaired as a consequence of the destruction of brain tissue, amounting to as much as 20 per cent of cells in animal brains. This is not true of all functions, but for many general functions of adaptation and learning it certainly is the case. If there are functional consequences for behavior that are a consequence of malnutrition, I would be quite doubtful about the likelihood of 10 to 15 per cent cell reduction being the mechanism for the production of behavioral alteration. This is not true when there are 50

and 60 per cent reductions such as those Dr. Winick and others have described.

It was argued that the Lashley evidence was irrelevant because ablation is quite different from growth failure or disturbance in brain caused by malnutrition. I would agree with Dr. Dobbing that what we need to know is more about the functional attributes of the nervous system, more about its refined structure, more about its intimate organization. His plea for the expansion of investigation of more complex integrative systems and intercellular organization is very well put, I think.

Dr. Winick has turned our attention in exactly the opposite direction. He wants to learn more and more about underlying mechanisms. What he is saying is that we can either move from the phenomenon of reduced cell number to a consideration of its consequences, or to a consideration of the mechanisms that produce fewer cells. He has directed his attention to the latter, and has explored a variety of enzymatic systems from particular features of protein synthesis to the relation of altered amino acid pools to such synthetic and degradation processes. His attention is therefore directed not at the consequences of malnutrition but at the subcellular-level mechanisms that may contribute to the organization of cellular system. This is important in and of itself. But he has a social conscience and therefore tries to extend its importance elsewhere, including diagnosis and the potential usefulness of particular proportion levels among enzymes as definers of nutritional status. I can only wish him well. At present I do not think that he has presented a convincing argument that they will be such useful indicators in defining nutritional status. We need such better indicators: there is every reason to want to be able to define the nutritional status of populations and individuals who are under stress. This may be a step in that direction, but I think only the future will tell us whether it is.

Dr. Stewart presented a most fascinating model of animal growth which to a very considerable extent parallels certain features of the human condition. He reports on generations of rats living at marginal subsistence levels, and his work makes it possible to analyze the intergenerational consequences of subsistence undernutrition. He has produced two populations of rats derived from a single stock, the first normal and the second the result of generations of undernutrition. These populations provide numerous exciting research opportunities. We can now explore the behavioral consequences of such different patterns of development in a genetically homogenous species. Since he does have selective survivals in his litters of organisms under stress, however, he must determine the extent to which genetically selective mechanisms have been operating. To do so he must carry out rehabilitation studies over several generations to define the degree to which the malnourished survivors are representative of the parental strain. That would also provide useful information that would permit us to determine whether the animals will return to previous levels of growth and function after several generations of improved nutrition. Comparative work with such recovered groups of animals would also help to define whether genetic heterogeneity had in fact been introduced as a consequence of selective survival. But the models themselves are engrossing. He can only be congratulated for his patience and skill in developing them.

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Session II

FUNCTIONING OF CHILDREN MALNOURISHED IN INFANCY OR FROM DISADVANTAGED SOCIAL BACKGROUNDS

Chairman

Michael Beaubrun

Rapporteur

Jack Tizard

EMPIRICAL FINDINGS WITH METHODOLOGIC IMPLICATIONS IN THE STUDY OF MALNUTRITION AND MENTAL DEVELOPMENT[1]

Robert E. Klein, Jean-Pierre Habicht, Charles Yarbrough, Stephen G. Sellers, and Martha Julia Sellers[2]

The study of the effects of protein-calorie malnutrition on intellectual development is a chronicle of investigators' attempts to estimate the effect of malnutrition per se, apart from the variety of other biologic and social factors that are also known to influence intellectual development. Our report describes a continuation of this line of research and presents data on psychologic test performance with independent estimates of variance contributions from social and biologic factors. Data recently collected in a longitudinal study of children suffering from mild to moderate protein-calorie malnutrition are presented and discussed.

Method

Subjects

The subjects of this study were children three through six years of age living in isolated, rural, subsistence-farming communities in eastern Guatemala. The numbers of subjects included in the analysis vary slightly with each psychologic test and are reported in Tables 1 through 4. The subjects are part of a continuing longitudinal study of the relation among malnutrition, physical growth, and cognitive development.

Variables measured

Three types of data were collected and are reported here: indices of physical growth, sociocultural information on the family and the environment, and psychologic test performance. The physical growth and psychologic test performance data were collected on the child's birthday plus or minus 15 days. The sociocultural characteristics of the family were measured over two years and represent a composite picture of the family during that period.

Physical growth. Two measures of physical growth are included in the present analysis, total height and head circumference. These

[1] This research was supported by Contract PH43-65-640 from the National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA.

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Table 1. Multiple correlations between height, head circumference, and psychologic variables.

Variable	Boys				Girls			
	N	r	Height	Head circum.	N	r'	Height	Head circum.
Verbal Analogies	138	.19	.08	.11	131	.18	.06	.12
Memory for Designs	51	.38	.00	.35	63	.40	.30	.14
Reversal Learning: Trials to Criterion	42	.20	.13	.11	37	.30	.03	.26
Response Time	42	.42	.10	.30	37	.26	.12	.17

Table 2. Multiple correlations between six social-class indices and psychologic variables.

Variable	Boys		Girls	
	N	r	N	r
Verbal Analogies	138	.25	131	.37
Memory for Designs	51	.36	63	.43
Reversal Learning:				
Trials to Criterion	42	.55	37	.35
Response Time	42	.70	37	.42

Table 3. Multiple correlations between height, head circumference, six social-class indices, and psychologic variables.

Variable	Boys					Girls				
	N	r	Height	Head circum.	6 SES	N	r	Height	Head circum.	6 SES
Verbal Analogies	138	.28		.17	.15	131	.37		.04	.36
			(.08)	(.11)	(.25)			(.06)	(.12)	(.37)
Memory for Designs	51	.43		.35	.32	63	.52	.27		.25
				(.35)	(.36)			(.30)	(.14)	(.43)
Reversal Learning:										
Trials to Criterion	42	.54			.54	37	.36			.21
			(.13)	(.11)	(.55)			(.03)	(.26)	(.35)
Response Time	42	.73		.07	.72	37	.42		.25	.28
			(.10)	(.30)	(.70)			(.12)	(.17)	(.42)

measures were chosen because they are frequently reported in the literature as indices of nutritional history.

Sociocultural family status. Six sociocultural indices were derived from a body of interview and observational data collected about the family of each subject. These indices reflect the material status, social interaction, and reported child-rearing practices and parental behavior. The specific indices and their component elements are: (1) housing (quality of the kitchen, bedroom, and dining area, number of rooms in the house, and the materials from which the roof and walls are constructed); (2) teaching (interaction of the mother, father, and siblings with the child in three activities: teaching the child to count, teaching him to do household tasks, and accompanying him to a nearby town); (3) occupation (father's occupation, scored on a two-point scale); (4) mother's clothing (regular use of a sweater and shoes); (5) mother's hygienic practices (frequency with which the mother washes her hands and face), and (6) sociability (number of visits both made and received by the family during the previous year). Except for the father's occupation, the indices were constructed by bimodal coding of the elements and summing.

Table 4. Projected increases in growth due to supplementation.

Variable	Projected increase at 7 years of age	Age-sex-specific standard deviation
Height	5.0 cm	4.0 cm
Head circumference	0.9 cm	1.3 cm

Psychologic tests. The psychologic tests reported here are part of a large psychologic test battery currently being applied in the longitudinal study of malnutrition and mental development. The four psychologic variables employed were chosen because they are commonly used tests and measure different aspects of psychologic functioning. They were Verbal Analogies, Memory for Designs, Reversal Learning, and the subject's response time in the Reversal Learning task. The first was a simple verbal analogies task cast in the form of a sentence-completion problem. In this 15-item test the examiner would read a sentence lacking the final word and the subject had to complete the sentence (e.g., "The skin on the pineapple is rough; the skin on the banana is _____"). This task was given to children from three through six years. In the Memory for Designs task the child had to reconstruct

a design from memory with multicolored blocks after having inspected the design for five seconds. Three consecutive trials were given on each design and scoring was by the number of blocks correctly placed with respect to the original design. This task was used with children five and six years. The Reversal Learning test was a two-choice, shape-discrimination learning task employing four blocks of 20 trials each. The child was rewarded for choosing one shape over another for blocks 1 and 2. In blocks 3 and 4, the other shape was arbitrarily designated "correct" and the child had to learn to reverse the previously made discrimination. Data on blocks 3 and 4 following the reversal of the discrimination are presented here.

Data analysis

The psychologic and physical growth variables were normalized within age-sex groups, and for those variables in which more than one age was represented, ages were combined and sexes were kept separate for all analysis.

The sociocultural data were treated in raw-score form and all indices were the combinations of simple raw scores. In all cases, the indices characterize the subject's family rather than himself.

For the multiple correlations involving both measures of attained size and social-class indices, only those variables that were statistically significant and accounted for 2 per cent or more of the variance in psychologic test performance were included.

Results

Table 1 presents the multiple correlations between total height, head circumference, and the four psychologic variables under consideration. For Verbal Analogies, the multiple correlations are essentially similar for boys and girls. Moreover, approximately equal amounts of the variance are contributed by height and head circumference, respectively, for both boys and girls. For the Memory for Designs test, the total multiple correlations between performance on this task and the two measures of physical growth are also essentially similar for boys and for girls, but there are differences in the amount of variance contributed by height and head circumference, respectively. Height contributes none of the variance to performance of the boys, whereas for girls it predicts performance more strongly than does head circumference. In the case of Reversal Learning, trials to criterion are better predicted for girls than for boys. On this measure, head circumference and height contribute about equally for boys, whereas for girls head circumference predicts performance better than does height. For response time on Reversal Learning, boys' performance is better predicted by the two physical growth measures than is girls', and head circumference predicts more of this performance for boys than does height. In contrast, both height and head circumference contribute about equally for girls.

The multiple correlations between the four psychologic variables and six social-class indices are presented in Table 2. Looking first at Verbal Analogies, we find girls' performance is better predicted than boys' by these indices. The same is true for Memory for Designs. For the Reversal Learning task, however, the tendency for girls' performance to be better predicted by social-class variables is reversed. In the last task both trials to criterion and response time are better predicted for boys than for girls by the six social-class indices.

To see the relative contribution of the two measures of physical growth and the six social-class indices, multiple correlations were computed between the four psychologic variables and height, head circumference, and the six sociocultural variables.

The results of these analyses are presented for boys and girls separately in Table 3. The numbers in parenthesis are the beta weights for the variables as they appeared in Tables 1 and 2. Looking first at the Verbal Analogies

test, we note that the multiple correlations for two physical growth variables and the six social-class indices are higher for girls than for boys. Of particular interest is the relative contribution of physical growth versus sociocultural factors. For boys, head circumference and the six sociocultural indices contribute about equally to the multiple correlation of .28, whereas for girls, the six sociocultural variables contribute the bulk of the variance to the multiple correlation of .37. Head circumference contributes relatively little and height contributes nothing.

For Memory for Designs, we see again that girls' performance is somewhat better predicted by the combination of physical growth and sociocultural indices than is boys' performance. The social-class indices contribute strongly to the multiple correlations for both sexes. In the case of boys' performance, however, head circumference contributes about the same as do the social-class indices, whereas for girls' performance height rather than head circumference contributes heavily to the variance in performance.

Turning now to the Reversal Learning task, we find that, as was the case for the physical growth and sociocultural variables considered separately, boys' performance is better predicted by the combination of physical growth and the social-class indices than is girls' performance. This is true both for trials to criterion and response time. For trials to criterion, the social-class indices contribute the major portion of the variance for both boys and girls. In the case of response time, however, the social-class indices contribute the bulk of the variance to performance for boys, whereas for girls both the social-class indices and head circumference contribute about equally to response time.

Discussion

There are three major points to be made from these data. First, there are differences associated with attained size, but they are complicated by sex differences in the patterns of performance and in the manner in which attained-size and social-class indices predict psychologic performance for boys and girls. Nonetheless, it is obvious that both attained-size and social-class indices used here are powerful predictors of psychologic performance.

The second point to be made from these data is the necessity for careful consideration of the type, range, and focus of the psychologic test to be employed in studies of this sort. That the obvious variability among the independent variables regressed against psychologic performance through their contribution to the variance of psychologic performance underlines the need to use a variety of psychologic indices. By using a variety of measures, the investigator can try to replicate his findings not only for single variables but also in the profile across a battery of measures. This becomes extremely important when we consider the complicated interactions such as those observed for sex of the child, sociocultural status, and the type of psychologic test. The great danger in using single or relatively few psychologic measures is that it is entirely possible to have chosen one with unusual interactions, leading to an erroneous interpretation.

For example, if we consider only Verbal Analogies and Memory for Designs, we would conclude that girls' performance is better predicted than boys' and that the social-class indices do not generally predict a dramatically greater amount of the variance in psychologic test performance than do the measures of attained size. When we include Reversal Learning in the analysis, however, we find that these generalizations do not obtain. Boys' performance is better predicted than girls' and the social-class indices contribute the bulk of the variance to boys' performance.

The third point deals with the nature of the measures of attained size and social class. Since the elaboration of these sociocultural indices is

essentially an empirical operation and is only very generally guided by theoretical considerations, it simply is not clear to what extent measures of attained size are also relatively good indices of social class and to what degree sociocultural indices are themselves reasonably effective estimates of nutritional status. Thus, although the isolation and partitioning of variance yields interesting and informative information about psychologic performance and its relationship to both attained size and social class, an experimental treatment is ultimately necessary if we are to understand the impact of malnutrition on mental development.

A successful experimental treatment, such as nutritional supplementation, must produce independently of social-class indices a sufficiently large change in growth to measure the contributions of these two variables with psychologic performance. In the longitudinal study discussed here, such comparisons will be possible given the present differences in growth velocity between supplemented and unsupplemented children. Table 4 presents the expected differences at seven years of age due to nutritional supplementation. Thus, with continued supplementation an answer to this problem will be forthcoming.

MALNUTRITION AND MENTAL CAPACITY

Fernando Mönckeberg[1]

Numerous data in the literature, based on animal experimentation and observations in humans, confirm that severe undernutrition in early life delays brain development (*1–9*). The occurrence of many biochemical alterations and clear retardation of mental development have been described during this period. Follow-up studies of animals or children who have suffered from severe early malnutrition have demonstrated that brain metabolism and mental performance are affected, and that in all probability this damage is definite (*3, 5, 9*).

In recent years marked interest has arisen in whether chronic undernutrition during the preschool or school years modifies behavior and mental capacity. This problem is of extraordinary importance because almost 70 per cent of the world's population now suffers from chronic undernutrition of varying degrees (*10*). If these statements are valid, it would be obvious that undernutrition constitutes one of the major obstacles to the progress of underdeveloped countries since for their advancement they need highly qualified individuals at all levels.

Different investigators have noted the fact that poor preschool children have reduced growth and a slower maturation rate (*3, 5*). A higher frequency of retardation of mental and motor development has also been observed at the same time. From current experimental data, it may safely be assumed that retardation of growth and maturation is the consequence of undernutrition. We cannot be so certain as regards mental and motor impairment. There are many environmental factors that may negatively influence intellectual capacity. Unfortunately, the social groups that suffer from malnutrition are precisely those that are outside the mainstream of society because they have very low educational, cultural, and sanitary levels. All these factors contribute to inadequate stimulation for mental development.

When studying groups of low socioeconomic status and intellectual performance, as in slum areas, a significant relationship between growth retardation and low intellectual capacity may be observed (Figure 1). A similar correlation may be seen between animal protein intake and intelligence quotient (Figure 2), so that those children consuming a smaller proportion of animal proteins have significantly lower intelligence quotients. This correlation is not observed when analyzing the total amount of caloric intake. In children under three years of age a significant correlation can also be observed between cranial growth retardation and intelligence quotient (Figure 3). This correlation ceases to be significant when cranial growth is within normal limits (*7*).

All these correlations, even though very suggestive, do not allow us to conclude that malnutrition per se is the cause of mental impairment. This is because even in slum areas of more or less homogeneous low-level population, it is to be assumed that children found to

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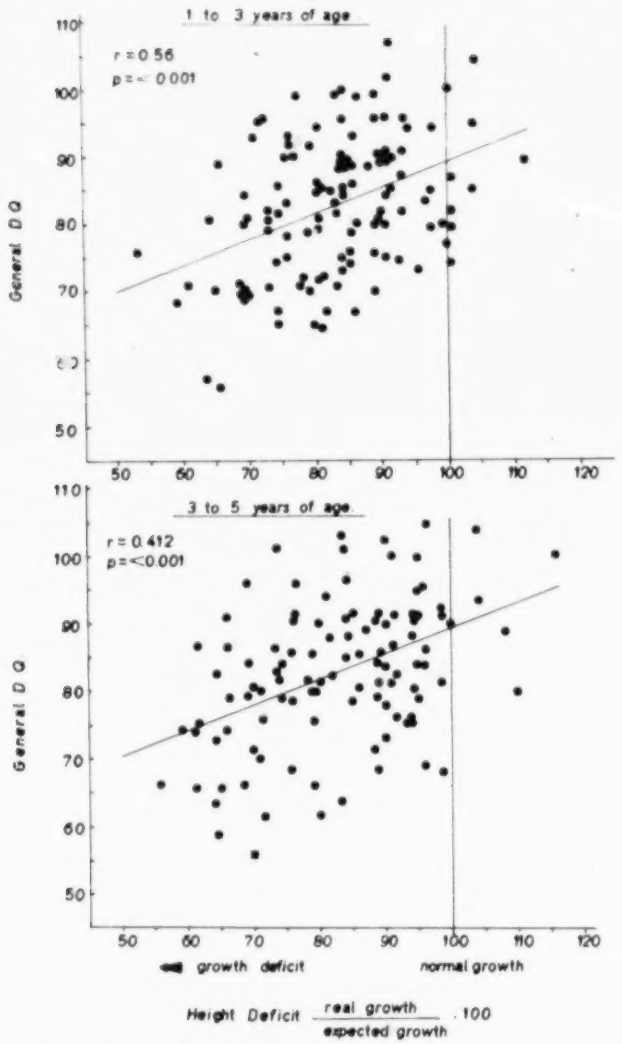
1 to 3 years of age
r = 0.56
p = < 0.001
General D Q
3 to 5 years of age
r = 0.412
p = <0.001
General D Q
growth deficit
normal growth
Height Deficit real growth / expected growth . 100

Figure 1. Height and mental development quotient in preschool children from 1 to 5 years of age.

be nutritionally normal come from better educated and better-off families. It is therefore possible that malnutrition could be a concomitant and not the cause of the impaired developmental quotient. On the other hand, even children with acceptable nutritive status have lower IQs than preschool children belonging to groups of a higher socioeconomic level.

At any rate, nutritional factors cannot be the only cause conditioning the high incidence of mental capacity deficit among the poor.

The high frequency of mental impairment is not only observed in preschool children, but it also affects school-age children in the same proportion. One of the main problems in Latin America during school age is the high per-

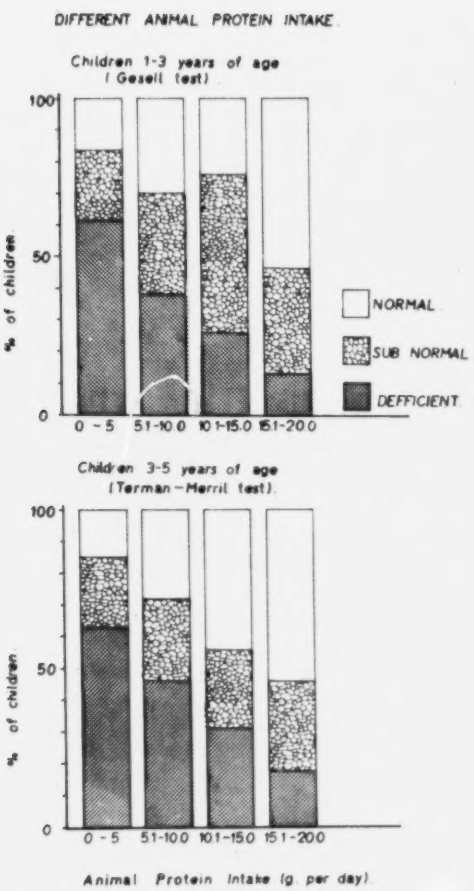

Figure 2. Percentage of mental normality, subnormality, and deficiency in preschool children with different animal protein intakes.

centage of dropouts; of 100 children who begin primary school, only 20 finish. It is probable that this higher dropout rate is due in part to learning difficulties and low mental performance.

During the past year we planned and carried out a study in a rural public school near Santiago, Chile. It was located in a poor, relatively homogeneous agricultural zone in which almost every father was a tenant farmer and not a land owner. One hundred sixty-six children were studied. They constituted a sample taken at random from the school's 800 students, whose ages ranged from six to 13 years. The following parameters were studied: (1) anthropometry and clinical signs of nutritional status; (2) the nutritional characteristics of each child and his family; (3) socioeconomic characteristics of the family that defined life conditions and the sociocultural environment; (4) the child's school performance, for an estimate of the amount of knowledge he had assimilated; and (5) the child's intelligence quotient, through the infantile Wechsler intelligence test.

The complete data are now being processed, but preliminary results indicate a high incidence of undernutrition and low mental performance. Table 1 shows some of the data from the different years of primary education. The number of students enrolled is high during the first and second years but decreases thereafter because of dropping out. During the first two years children had an average height deficit, in relation to age, of 10 per cent compared to the Iowa Scale's 50th percentile. In later school years this deficit was only 3 per cent. The same thing can be seen as regards weight—the first years showed a deficit of 15 per cent and the later ones only 3 per cent. The intelligence quotient was low during the first and second years and increased during the following years until reaching an average value of 101 in the seventh and eighth years. Something similar happened with school performance, which increased significantly during the later years.

For the same group of children we developed a "cultural deprivation" index in which the following parameters were considered: education of the mother and father, IQ of the mother, and the family's access to mass communications media (television, radio, newspapers, and magazines). Significant correlations were observed between the intelligence quotient and the degree of cultural deprivation ($p <$

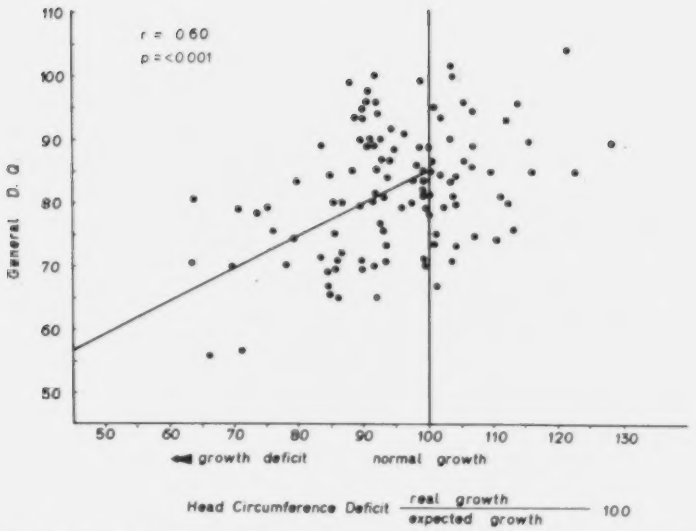

Figure 3. Head circumference and mental development quotient of preschool children 1 to 3 years old.

.01), growth retardation ($p < .05$), and consumption of minimal proteins ($p < .01$).

We are now studying the group of children who left school prematurely and even though we have no definite results, it seems clear that these dropouts have a lower intelligence quotient than children of the same age who continue in school.

All these observations seem to indicate that the low intellectual performance so frequently observed in the poor seriously interferes with school performance and probably determines dropping out. From the data so far analyzed we cannot conclude the degree to which undernutrition or cultural deprivation influences mental development.

Two years ago, we tried to see if a school child's low intellectual performance could be modified by appropriate feeding. With this object we chose 60 poor children aged seven to nine years who were small for age. They received three meals at school adequate for total food requirements. The trial lasted the nine school months, and the children's intelligence quotients were measured at the beginning, fourth month, and end of the trial (Table 2). During this period a normal increase in weight and height could be observed, but there was no change in the high frequency of intellectual deficiency. Even though the observation period was relatively short, it would appear that adequate nutrition during

Table 1. Nutritional, physical, and intellectual correlates of children in the Alto Jahuel Primary School near Santiago, Chile.

School year	1st/2nd	3rd/4th	5th/6th	7th/8th
Number of students	403	260	160	80
Height deficit for age (avg.)	10%	7%	7%	3%
Weight deficit for age (avg.)	15%	8%	9%	3%
Caloric deficit for age (avg.)	16%	10%	10%	+2%
Animal protein deficit for age (avg.)	32%	20%	17%	6%
IQ (Wisconsin) (avg.)	81	87	92	101
School performance	50	57	60	66

Table 2. Intelligence quotient, weight, and height of 60 school children (7 to 9 years old) during nine-month period.

Period of study		Month 0	Month 4	Month 9
IQ (Gille)	Normal (>91)	9%	11%	8%
	Subnormal (80-89)	50%	44%	48%
	Deficient (<79)	41%	45%	44%
Weight increase (avg.)		0	1.8 kg	2.7 kg
Height increase (avg.)		0	2.3 cm	4.1 cm

the school years does not improve intellectual capacity. It may be postulated that psychologic deficit is due mainly to factors other than nutritional ones (e.g., sociocultural factors), or that the damage produced by undernutrition before this time is irreversible.

A very interesting experiment with preschool children is now taking place in Cali, Colombia, under the supervision of Drs. Leonardo Sinisterra, and Harrison and Arlene McKay. I have participated in it as a consultant. Three-year-old undernourished children from a slum area of the city have been selected and entered in a program of physical and cognitive stimulation while simultaneously being adequately fed. As a control, another group of children of the same age and nutritive and socioeconomic status have been receiving an adequate feeding at home but no stimulation. The program has so far been in operation only one year, but the results seem to be clear. While both groups have gained physically according to norm, only the stimulated group has improved significantly in intellectual development, achieving after a year values very similar to those of Colombian middle-class preschool children. This indicates that the impairment of mental development may be reversible at this age, though feeding alone is not sufficient to increase mental development—at least in a period of only one year.

Of all the factors analyzed, it seems obvious that the poor intellectual performance observed in low socioeconomic groups cannot be attributed only to malnutrition, but must also and in a very important way be ascribed to sociocultural factors that interfere with adequate stimulation during the first years of life. Malnutrition is never an isolated phenomenon, and it is almost impossible to analyze separately the importance that each factor contributes to intellectual retardation and thus obtain a definite answer. The important thing to know is not so much the mechanism that produces mental impairment but the fact that this really exists and that it interferes very severely with the individual's and therefore with society's development. Poor intellectual performance interferes with learning processes and education in general, preventing children from reaching adequate educational and cultural levels and thus being wholly incorporated in the socioeconomic development of the country.

It may also be concluded that it is too late to correct mental impairment after seven years of age. Neither adequate feeding nor conventional education improves mental performance in any important way. Instead, very good results seem to be obtained if stimulation and adequate nutrition start during the first three years of life.

An inadequate environment, from a sociocultural as well as a nutritional viewpoint, evidently lessens the child's developmental possibilities when he enters school and good performances during the school years are very difficult to obtain.

It seems evident that programs of stimulation and education should start during the first years of life so that the child may later perform adequately in school. Nevertheless, we must recognize that an adverse environment is a very difficult obstacle to overcome. We have measured the intellectual quotient of mothers

in different slum areas in Santiago and have found a high frequency of mental retardation (Table 3). Seventy per cent of the mothers had an IQ under 79 when studied with the Terman-Merril test, while middle-class mothers showed much higher IQs, none of them scoring below 79.

A very close relationship was observed between the mother's IQ and the growth status of her children ($p < .001$) (Figure 4): the lower her IQ, the worse the nutritional status of the child. This fact is extremely important and shows that a correlation exists between inadequate cultural environment and nutrition. This is a vicious circle that explains why mental impairment persists from one generation to another and offers very few possibilities for the individual to escape from it. The only solution is to create a new and different environment for the child in which he may receive appropriate stimulation, education, and nutrition from the first years of life. More research is needed in this field, but given present knowledge it seems that this is the only way to really get to the heart of the problem and obtain rapid changes from one generation to another.

Table 3. Intelligence quotients of slum-area and middle-class mothers.

	Slum area (%)	Middle class (%)
Normal (>91)	6	96
Subnormal (80-89)	17	4
Deficient (<79)	77	0

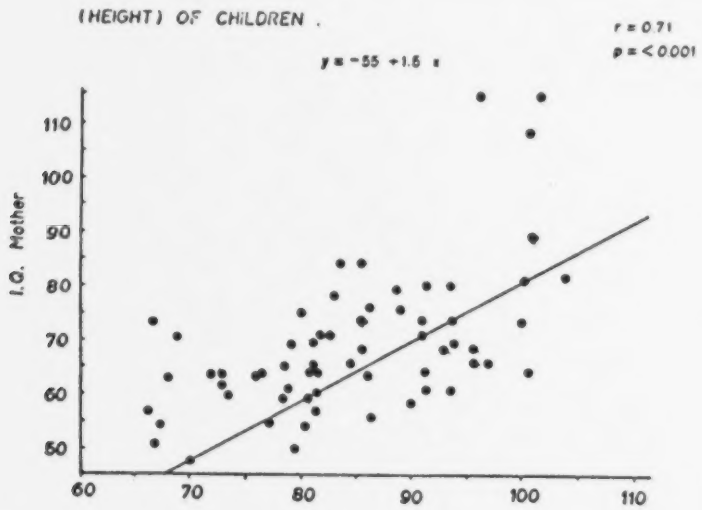

Figure 4. Intellectual quotient of mothers (Wechsler-Bellevue scale) and growth (height) of children ($r = 0.71$, $p = < 0.001$).

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THE INFLUENCE OF MALNUTRITION ON PSYCHOLOGIC AND NEUROLOGIC DEVELOPMENT: PRELIMINARY COMMUNICATION[1]

Jan Hoorweg[2] and Paget Stanfield[3]

The long-term effects of malnutrition on human and animal development have captured considerable attention over the last few years. Although much is written and a number of congresses have been held on this subject, facts are comparatively scarce, particularly in respect to psychologic development. The most striking effects have been found in animal experiments but the results with human subjects are hardly as impressive. The indications that a period of malnutrition hampers a child's development are so strong, however, that many researchers no longer pose the question whether malnutrition influences development but look into more specific questions such as how, when, and under what conditions malnutrition affects development.

Retrospective and Prospective Studies

In its simplest form the problem requires the comparison of malnourished and well-nourished subjects. Two major research strategies are possible—prospective and retrospective studies. A prospective or longitudinal study is often considered preferable because it is expected that other variables influencing development can be better controlled than in a retrospective study. Huge efforts may be spent in obtaining results that are outdated by the time of publication, however. There is also the difficulty that because of the very observations that have to go into a longitudinal study to control other variables, cases of malnutrition are much earlier detected and consequently earlier treated. Before starting on a longitudinal study baseline knowledge is needed. This baseline can be obtained in retrospective studies.

As malnutrition most often occurs in areas where records of cases are hard to obtain, even the collection of subjects is difficult. To take a known result of malnutrition such as shortness of stature as indicative of it is a very dangerous procedure, as Richardson (9) has convincingly argued. It is at least necessary that the groups to be compared differ decisively on the variable of nutrition. This not only poses the problem of obtaining a group that has suffered from malnutrition, but also a group known not to have suffered from malnutrition, which is perhaps even more difficult.

Since 1953 the British Medical Research Council has run a research unit, until recently called the Infantile Malnutrition Unit, in Kampala, Uganda. Up to 1962 some 1,000 patients were treated there. Most of them were

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drawn from a rural clinic at Namulonge, some 19 km from Kampala, where later they were also followed. At the same clinic many reasonably normal children were regularly seen. The clinic kept and carefully preserved records of all persons seen, and from the records a group of patients and another of controls were selected.

Design

Selection of malnourished patients (Groups 1–3)

It has been strongly suggested that the effects of malnutrition are greater the more severe the illness and the younger the age of the child when malnutrition occurs. Following are the study's design features:

(*a*) *Age at occurrence of malnutrition.* Three groups of 20 patients each who had been admitted to the clinic at different ages were selected and matched (see below) with each other and a control group. Any doubt or discrepancy about the child's date of birth that could not be clarified by checking the birth registers excluded a child from selection. Group 1 consisted of patients who had been admitted before 16 months of age (average admission age, 12.6 months). Group 2 patients had been admitted between the ages of 16 and 21 months (average, 18.7 months). Group 3 patients had been admitted between 22 and 27 months of age (average, 24.1 months).

(*b*) *Severity of malnutrition.* Details of clinical admission and progress were scored according to (1) overall clinical impression, made and recorded at the actual time of discharge; (2) the admission weight as a percentage of the Baganda mean; (3) the amount of edema; (4) skin changes, and (5) the total serum protein level. Although severity of malnutrition was not taken into account in matching, the average severity scores of the three malnourished groups do not differ (Table 1).

Table 1. Composition of groups.

		Malnutrition			Controls
		−15 months	16-21 months	22-27 months	
	Group	1	2	3	4
	N =	20	20	20	20
Subjects	Age (average in years)	14.1	14.0	13.8	13.9
	Educational level (average in years)	4.6	4.5	4.4	4.4
	Severity of malnutrition	17.1	16.9	17.5	—
Male guardian	Education:				
	reached senior or primary 5,6, or 7 level	41%	56%	47%	56%
	Occupation:				
	farmer	65%	35%	89%	55%
	trader or semiskilled	35%	60%	—	30%
	white-collar worker	—	5%	11%	15%
Female guardian	Education:				
	reached senior or primary 5,6, or 7 level	40%	34%	12%	35%
Family	Lives in house:				
	with mud walls and floor	50%	75%	80%	60%
	no. of rooms (avg.)	5	4.4	3.7	4.0
	Has:				
	dining table	85%	89%	70%	60%
	radio	65%	79%	55%	55%
	bicycle	55%	58%	45%	35%

(*c*) *Age group.* Children were selected who were separated from their episode of malnutrition by the longest possible period of time. The age of the subjects ranged from 11 to 17 years. They had suffered from malnutrition nine to 15 years previously.

(*d*) *Type of malnutrition.* Malnutrition may be either edematous (kwashiorkor) or marasmic. In Buganda the clinical presentation is nearly always a mixture of both.

(*e*) *Duration of malnutrition.* Histories are notoriously unreliable and would have been of little use in assessing the period over which the child had suffered from malnutrition before admission. Almost all the children recovered fairly rapidly. Follow-up continued for a few weeks or months after discharge. Each child had one attack of clinical malnutrition.

(*f*) *Associated conditions* occurring during the period of acute malnutrition. Children who had had any possible acute brain insult such as convulsions or severe respiratory infection with anoxia were excluded, as were those with long-term chronic infections such as tuberculosis. Severe anemia did not exclude a child unless a disturbance of consciousness or convulsion was recorded.

(*g*) *Genetic factors* could not be controlled. Sib controls were too few, and too different in age, education, environment, and upbringing. Besides, the family and social structure are such that uncertainty always exists as to the true genetic constitution of the sibs.

Selection of controls (Group 4)

The controls were children who had attended the outpatient clinic and had not suffered a clinical attack of malnutrition. The criteria for their acceptance in regard to the critical variable of nutrition were a recorded follow-up of at least two years beginning in the first year of life and a weight curve that did not fall below the Boston tenth percentile during the recorded period. In fact, three children ultimately chosen did fall below the tenth percentile on one occasion each and one of them fell below the third percentile. Notes recorded at the times of these falterings did not mention any signs of clinical malnutrition.

As in the groups of malnourished children, those who had had severe illness that might have adversely affected mental development were excluded.

Matching

Numerous variables affect physical and mental development. In a study such as this, care must be taken that the experimental variable (malnutrition) is not confounded with other variables. The cultural background of the subjects in this study was kept constant—only Baganda children were included. Patients under the age of 16 months were relatively few; individuals in the other groups were matched with individuals in this group, as nearly as possible, on the following variables (Table 1):

(*a*) *Age.* The average age for groups 1, 2, 3, and 4 was 14.1, 14.0, 13.8, and 13.9 years, respectively.

(*b*) *Sex.* Each group consisted of 11 boys and nine girls.

(*c*) *Environment.* Stimulation provided by the environment is a major factor in psychologic development. The following aspects were taken into account:

(*1*) *The child's educational level.* The average education of the four groups based on the primary grade reached by each child was 4.6, 4.5, 4.4, and 4.4, respectively.

(2) *Socioeconomic status.* Information on education guardians, male guardian occupation (when there was no male guardian living with the child, the female guardian was regarded as such), and several indicators of economic prosperity are presented in Table 1.

Some of these indicators show considerable variation among groups, but there are no systematic differences. The average scores over the three malnourished groups are not noticeably different from those of the controls.

Examinations

Five groups of examinations were carried out, the first a battery of psychologic tests given by one of the authors, usually outside the child's home in a Volkswagen bus converted into a test vehicle. Later the child was brought to the clinic for clinical and neurologic examination, anthropometric measurements, hemoglobin and total serum protein estimation, motor development assessment.

Psychologic examination

A variety of tests thought suitable for this particular group of subjects and this particular problem was used:

The Raven Matrices is generally considered one of the tests coming closest to measuring a general intelligence factor (*10*). The test has proved valuable in different African cultures (*5*, *14*). Subjects have to choose one of six pieces to complete a pattern, and in this case the board form of the Coloured Matrices was used (*7*). Vernon (*12*) factorized scores on some 20 tests covering a wide range of abilities among 12-year-old Ugandan schoolboys. He found a strong verbal factor, a general intelligence factor or induction, and a practical or performance factor composed of spatial and perceptual abilities.

Two tests were used for assessing verbal abilities. The arithmetic test of the WISC was adapted and a test of Luganda words and idioms (vocabulary) was developed.

Block Design (WAIS) and Porteus Mazes (*1*) were selected for measurements of spatial and perceptual abilities. In the Block Design test, subjects have to copy a diagram with colored blocks. Time limits for this test were doubled. In the Porteus Maze test subjects have to draw the correct way out of each of a number of mazes. This test was given in an abbreviated form.

The Memory for Designs test (*4*) consists of 15 cards with simple patterns, each of which is shown the subject for five seconds, after which they have to draw the patterns from memory. This test of visual memory has been developed for diagnosis of organic impairment and has been standardized on normal and brain-damaged groups in the United States.

Klein (*6*) has reported that formerly malnourished patients sometimes did poorer than controls in a short-term memory task, the Knox Cubes (*1*), if the presentation was performed quickly. Both normal and quick presentation were used in this study. Subjects have to repeat the order and number of taps on four cubes.

To gauge learning and incidental learning, subjects were instructed to memorize associations between six animals and six colors. Two series of colors were used, colors having different shapes in each series. Therefore each color was presented on two shapes, there being 12 shapes in all. The instruction did not mention shapes, but concentrated instead on the association color-animal that had to be memorized. Subjects were given four trials (one trial consists of both series), errors were corrected, and responses were recorded. On completion of this part subjects were presented with the 12 shapes and asked to remember the color of each shape. This then is a measure of incidental learning.

For motor development assessment, use was made of the Lincoln-Oseretsky Motor Development scale (*11*). The test consists of 36 increasingly difficult motor tasks involving balance, dexterity, coordination, and rhythm. Scores are based on accuracy of accomplishment and often on speed of completion.

Results

It must be emphasized that this presentation of results is preliminary, and that there is a considerable amount of detailed analysis still to be done. Result have yet to be compared with other findings in the literature.

The clinical examination of all the children revealed no serious disease. One child had an acute pyomyositis, which delayed the assess-

ment of motor development for two weeks. The spleen was palpable in 11 children scattered among all four groups. There was a considerable amount of tineal skin infection and resulting slight lymphadenopathy. Two children had old poliomyelitis, one involving the right shoulder girdle and arm, and the other the right leg. Hemoglobin and serum protein levels were all within normal limits and the mean values were similar in all four groups. An estimate of the stage of each child's puberty was attempted, and the scatter from prepubertal to postpubertal was similar in the four groups. Two of the oldest girls were pregnant and one in the control group was nursing a three-month-old baby.

Tables 2 and 3 give the means per test for each of the malnourished groups and for the controls. Results of the analysis of variance, randomized block design (*2*), are presented in Tables 4 and 5.

To have independent comparisons, orthogonal contrasts were constructed. As it was hypothesized that the effects of malnutrition would be inversely related to the age of occurrence, the following comparisons were chosen: controls (Group 4) were compared with the three malnourished groups taken together; the group that had suffered after 21 months (3) was compared with the two earlier groups (1 and 2); and the middle group (2) was compared with the group that had suffered before 16 months (1).

Malnutrition
(controls versus three malnourished groups)

Height, weight, and head circumference were significantly greater in the controls (Table 4). Differences on the external interiliac diameter come close to being significant ($F = 3.81$, $p < .10$). Mid-upper arm circumference and

Table 2. Anthropometry: means per group.

	Malnutrition			Controls
	−15 months	16-21 months	22-27 months	
Group	1	2	3	4
Height (cm)	146.7	145.6	143.4	150.1
Weight (kg)	38.5	39.4	38.4	43.8
Head circumference (cm)	53.3	53.5	53.3	54.2
Mid-upper arm circumference (cm)	21.7	22.0	21.7	22.4
Triceps skinfold thickness (cm)	6.8	7.3	6.4	7.2
Subscapular skinfold thickness (cm)	6.5	7.5	7.0	7.0
External interiliac diameter (cm)	21.6	21.4	21.3	22.3

Table 3. Psychologic tests: means per group.

	Malnutrition			Controls
	−15 months	16-21 months	22-27 months	
Group	1	2	3	4
Raven	24.5	23.5	23.1	25.9
Vocabulary	8.4	9.3	9.7	9.7
Arithmetic	8.8	9.7	9.6	9.3
Block Design	17.1	15.7	16.4	21.7
Porteus Mazes	6.4	6.3	6.2	7.0
Knox Cubes				
slow	10.1	10.4	10.9	10.6
quick	8.4	8.9	9.5	9.0
Memory for Designs (errors)	7.1	8.7	4.4	4.7
Incidental Learning	4.0	5.1	4.7	5.9
Lincoln-Oseretsky	104.2	102.5	107.1	114.0

Table 4. Anthropometry: results of independent comparisons, analysis of variance, randomized block design (F 1,57).

Groups	Comparison 2 vs. 1	3 vs. 1,2	4 vs. 1,2,3
Height	—	—	F=7.07 p< .02
Weight	—	—	F=8.85 p< .01
Head circumference	—	—	F=4.72 p< .05
Mid-upper arm circumference	—	—	—
Triceps skinfold thickness	—	—	—
Subscapular skinfold thickness	—	—	—
External interiliac diameter	—	—	F=3.81 p< .10

Table 5. Psychologic tests: results of independent comparisons, analysis of variance, randomized block design (F 1,57).

Groups	Comparison 2 vs. 1	3 vs. 1,2	4 vs. 1,2,3
Raven	—	—	F=4.53 p< .05
Vocabulary	—	—	—
Arithmetic	—	—	—
Block Design	—	—	F=6.98 p< .02
Porteus Mazes	—	—	—
Knox Cubes			
slow	—	F=3.44	—
quick	—	p< .10	—
Memory for Designs	—	F=5.28 p< .05	—
Learning	F=4.22	—	F=3.56
1st Trial	p< .05		p< .10
Incidental Learning	F=3.20 p< .10	—	F=5.83 p< .02
Lincoln-Oseretsky	—	—	F=7.86 p< .01

triceps and subscapular skinfold thickness showed no noticeable differences.

On the psychologic tests controls did significantly better on Raven, Block Design, Incidental Learning, and Lincoln-Oseretsky (Table 5). The results of the learning task at each trial are presented in Figure 1. Although differences are in the expected direction, neither on overall score nor score at each trial do they reach significance. It is only on the first trial that there is an indication of differences between Group 4 and Groups 1, 2, and 3 ($F = 3.56$, $p < .10$).

On the Memory for Designs test comparison between Group 3 and Groups 1 and 2 does reach statistical significance ($F = 5.28$, $p < .05$), but the comparison controls versus malnourished groups does not. Inspection of the means (Table 3) for each group shows that this can be explained by the fact that Group 3 is doing very well, which reduces the differences between controls and malnourished patients. From the means it appears that Groups 1 and 2 are doing less well than the controls. Differences were not significant on Vocabulary, Arithmetic, Porteus Mazes, and Knox Cubes.

Age of admission

Comparison of the three groups that suffered from malnutrition at different ages

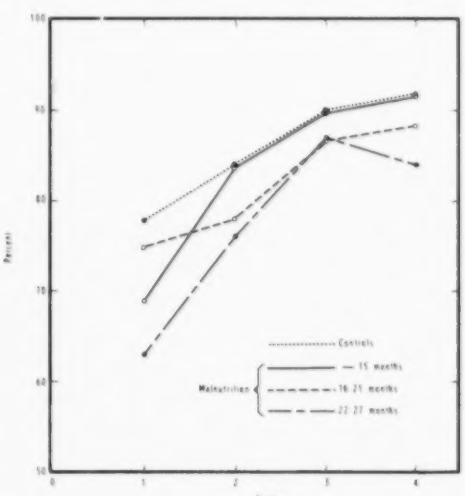

Figure 1. Correct percentage of responses per trial for different groups.

yielded no significant differences except for the Memory for Designs test, on which Group 3 did better than Groups 1 and 2, and the learning task (first trial), on which Group 2 did better than Group 1. Two other psychologic tests, Incidental Learning and Knox Cubes (quick), yielded differences that reached a significance level of .10. It should be noted that these four tests are all concerned with different aspects of memory and learning.

For the psychologic tests average scores per test for each of the three groups were ranked 1, 2, and 3. Inspection of Table 6 shows that overall this ranking distribution can be attributed to chance; but that on the tests concerned with memory and learning the average score of Group 3 is on all four tests higher than that of Group 1. These differences are in the expected direction in that those who suffered younger do poorer.

Severity of malnutrition

Because the three malnourished groups are not independent but matched, they cannot be combined for a comparison of severity of the malnutrition episode. Comparisons can only be carried out within each malnourished group. In each of the three groups cases were divided into two groups according to the severity of the malnutrition episode, thus yielding three severe groups and three less severe groups of 10 subjects each. Although detailed analysis has still to be done, there appear to be no differences between severe and less severe subjects.

Table 6. Ranks of means for malnourished groups per test.

	−15 months	16-21 months	22-27 months
Group	1	2	3
Raven	1	2	3
Vocabulary	3	2	1
Arithmetic	3	1	2
Block Design	1	3	2
Porteus Mazes	1	2	3
Memory for Designs	2	3	1
Knox Cubes	3	2	1
Learning	3	2	1
Incidental Learning	3	1	2

Discussion

Differences in height, weight, and head circumference have repeatedly been demonstrated in follow-up studies of malnourished patients. These retardations confirm that the control and experimental groups are different in nutritional history.

It appears then that the children who suffered an episode of protein-calorie malnutrition are lower in general intelligence than the control children. If there is a relationship between malnutrition, brain growth, and mental development, one would expect, on the basis of the literature on European subjects, that tests for spatial and visual abilities would show greater differences than tests for verbal abilities (*10*, *13*). The Block Design especially is often regarded as a very sensitive test in this regard (*8*). Results are in line with these expectations. Tests for verbal abilities show no differences, but the Block Design test does. That the second performance test, the Porteus Mazes, does not yield any differences may possibly be attributed to the fact that an abbreviated form of this test was used that gave a very small range in scores. It does not appear, however, that these differences can be attributed to *severe* brain damage. Although Groups 1 and 2 score higher in errors than Groups 3 and 4 on the Memory for Designs test, the average score of Groups 1 and 2 still falls below the average score reported in the United States for various groups of patients suffering from brain disorder (*4*). It is most likely that differences on the Block Design and Memory for Designs tests have to be attributed to poorer spatial and perceptual abilities; on the Memory for Designs, poorer memory or attention or both could also play a role.

Differences on memory and learning tasks seem to appear only with slightly complex stimuli. The Knox Cubes test uses simple stimuli (taps on blocks), and there are no differences between controls and malnourished

groups. Although differences on the learning task were not significant, differences between controls and malnourished patients tended to be largest on the first trials. This could indicate difficulties in attention rather than memory. The significant differences on incidental learning also indicate a limited field of attention.

The Lincoln-Oseretsky Motor Development Scale samples a variety of motor skills. Items can easily be divided into groups of balancing and dexterity skills. When the total score is broken down into subscores for balance and dexterity, it is only on the latter score that controls and malnourished groups differ significantly ($F = 7.92$, $p < .01$).

Defects in attention, spatial and perceptual abilities, and hampered fine-motor development are also features of the "minimal brain dysfunction syndrome" or the "cerebral minimal syndrome" (3), and as such could be the result of minimal, widespread cerebral cortical damage at the time of the attack of malnutrition.

That little difference was found between different groups of patients indicates that an attack of malnutrition in itself is so serious that age of occurrence or severity of the disease were of little importance for further development.

Summary

Three groups of 20 children each who had suffered an acute episode of malnutrition at three age periods, up to 15 months or from 16 to 21 months or 22 to 27 months were compared with a group of 20 control children from the same area of Uganda and of the same tribe, sex, age, education and socioeconomic status who, from evidence of clinical and weight records, had not passed through any overt period of malnutrition in early childhood.

All the children were between the ages of 11 and 17 and were examined clinically and neurologically, measured anthropometrically, and subjected to a battery of psychologic tests and a motor development test.

An analysis of variance between the groups of previously malnourished children revealed no significant differences in anthropometry, and on only two tests (Incidental Learning and Memory for Designs) did children who suffered young do significantly poorer than those who suffered from malnutrition at a later age.

Weight, height, and skull circumference were significantly greater in the control group than in the three malnourished groups together. Five of the 10 psychologic tests revealed significantly better performance in the control group as compared with the three malnourished groups taken together. These were the Raven Matrices as a measure of general intelligence, the Block Design test, Memory for Designs, incidental learning, and the dexterity part of the Lincoln-Oseretsky motor development scale. No differences were found on verbal abilities, a maze test, and a short-term memory test.

These results suggest an impairment in general intelligence, spatial abilities, memory, and learning arising from lack of attention and in dexterity in the subjects who had had an acute episode of malnutrition in early childhood, as compared to a group who had escaped such an incident.

This impairment is not of the magnitude that occurs in known syndromes associated with severe brain damage, but there is a resemblance to the so-called "cerebral minimal" syndrome.

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THE FUNCTIONING OF JAMAICAN SCHOOL CHILDREN SEVERELY MALNOURISHED DURING THE FIRST TWO YEARS OF LIFE[1,2]

Herbert G. Birch and Stephen A. Richardson[3]

Introduction

This is a report of a study conducted in Jamaica, West Indies, on the long-term consequences of severe malnutrition during the first two years of life. Our subjects were school children hospitalized during their first 24 months for severe clinical malnutrition (marasmus, kwashiorkor, or marasmic kwashiorkor). They have been compared with two groups of school children of like sex. The first comparison group consisted of the patients' sibs closest in age to the index patient. The second comparison group was composed of unrelated classmates or neighbors closest in age to the index child or the sib.

The concerns and design of the study stem from problems in interpretation and questions that arose in previous investigations of the effects of early malnutrition upon physical and mental development. Until recently few children who were severely malnourished in infancy survived to reach school age. Early research in malnutrition quite properly was focused primarily on its physiologic effects and on the development of treatment and management procedures that would prevent death and maximize recovery. As Champakam and coworkers (*12*) have put it: "Survival was the main concern. Awareness and knowledge of the biochemical pathology of malnutrition and the availability of more efficient means for better diagnosis and treatment have reduced the immediate mortality among malnourished children. In direct proportion to the success in this regard is the clear possibility of increasing pools of survivors who may be handicapped in a variety of ways and for variable periods of time" (page 844).

These changed circumstances have, over the past decade, resulted in a growing number of investigations exploring the long-term conse-

[1] The studies described here were carried out in Jamaica in the Tropical Metabolism Research Unit of the Medical Research Council. The investigations also received active support from the Epidemiology Research Unit of the Medical Research Council in Jamaica. Though most patients had been treated initially in the Tropical Metabolism Research Unit, additional patients, particularly in the youngest age group at hospitalization, were obtained with the help of the Department of Paediatrics, University of the West Indies. Follow-up studies included anthropometric, pediatric, neurologic, psychologic, educational, and social evaluations. Different aspects of the inquiry will be considered in separate reports.

[2] Support for this study was provided by the Association for the Aid of Crippled Children; The Nutrition Foundation, Inc., New York; Grants HD-00719 and NIH-71-2081 from the National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland; the Medical Research Council, London, and from program support to the Child Development Research Unit, Institute of Education, University of London.

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quences of both severe acute malnutrition and "chronic subnutrition" (*10*) for growth and intellectual development. In addition, numerous experimental animal models for studying such consequences have been employed (*30*). In studies of human subjects where controlled deprivation experiments could not be undertaken, follow-up studies have been conducted on children about whom both direct or indirect evidence of malnutrition has been available.

Two types of study designs have been used to explore the consequences of malnutrition for cognitive functioning in children. In some studies the presence of antecedent malnutrition in school-aged and preschool children has been inferred from differences in height for age. In communities where the risk of malnutrition is endemic, short children have been judged to have been at greater nutritional risk than taller age-mates. Groups of tall and short children have then been compared as to IQ level and intersensory competence (*17, 19*). The absence of direct evidence of severe malnutrition and the wide range of variables other than nutritional ones that differentiate the families of tall children from those of short ones (*18, 26*) have made it difficult directly to attribute the differences between the tall and short groups to malnutrition per se.

In the second type of study children with known histories of severe malnutrition have been compared with children in their communities without such histories (*5, 8, 11, 12, 14, 16, 23, 25, 27, 31, 32*). While the fact of antecedent malnutrition has been clearly established in such studies, other factors limit the degree to which they can be interpreted as indicating a direct association between antecedent malnutrition and intellectual outcome. Children who are severely malnourished early in life come from families that are at greater risk for disorganization, cultural limitation, social and economic disadvantage, poor housing, excessively frequent and short-spaced reproduction, maternal and child ill-health, and the like, than are other families of even the same social class (*18*). These additional factors themselves are capable of influencing intellectual development (*6, 24, 29*). In all instances the children with whom index cases have been compared could not be sufficiently well-matched on these nonnutritional variables to meet the requirements of rigorous experimental design. The most thorough attempt has been that of Champakam and coworkers (*12*) in which age, sex, religion, caste, socioeconomic status, family size, birth order, and parental education were taken into consideration. In that study, however, it was possible that the families of children hospitalized for kwashiorkor were either genetically different, or provided less adequate experiential opportunities for intellectual development than the comparison families (*6, 18*).

Another tactic is to use sibs of the malnourished children as comparisons. Such sib studies, though admittedly imperfect, provide different opportunities for interpreting findings. Only two such sib studies have thus far been carried out (*7, 22*). In one of these (*7*), sibs without a history of hospitalization for severe nutritional illness were found to be significantly superior in IQ to their hospitalized brothers or sisters. The conclusions from this study are limited, however, by the facts that the sample studied was relatively small, the sibs were not like-sexed, and no general population comparison group was examined. In the other sib study (*22*), the age at which malnutrition was experienced ranged from 10 months to four years, and only 10 of the children in the group were under 18 months of age. Moreover, gross differences in IQ in different segments of the kwashiorkor sample as well as in their siblings make the data difficult to interpret.

In conducting a sibling comparison study it must be recognized that while sibs may have many background characteristics in common, a number of differences must be considered in the analysis of findings. Sibs, unless twins, are necessarily different in age and ordinal position, both of which factors may affect child-rearing practices as well as intellectual outcome (*3*).

Moreover, in a community such as Jamaica sibs frequently have different fathers and experience different child-rearing conditions. These factors must all be taken into account in designing and interpreting a sib comparison study. This has been attempted in the present study.

A second question with which the present study is concerned has emerged from both reports of animal investigation and studies of recovery in children who were hospitalized for severe malnutrition at different ages in early life. The evidence of the animal investigations indicates that the risks of defective myelination, reduced cell replication, and delayed biochemical maturation are greatest when malnutrition coincides with particular periods of rapid brain growth (*13, 20, 21, 34*). In the human organism the period of most rapid brain growth extends from about the beginning of the last trimester of pregnancy to the last quarter of the first postnatal year. Moreover, during this period cellular replication in the central nervous system is completed.

These facts have led to speculation that severe malnutrition during the first nine months after birth would have more severe consequences than severe malnutrition later in infancy and early childhood. Some support for these expectations has derived from a study by Cravioto and Robles (*16*) in which children hospitalized with severe malnutrition in the first six months of life were found, during convalescence, to recover behavioral competence less fully than children hospitalized for the same illness later in infancy. For several reasons, however, these data are by no means conclusive. Although cell replication is completed at an early age, other aspects of growth and differentiation in the nervous system such as dendritic proliferation, axonal branching, and synapse formation, all of which may be more important for integrative organization than cell number, continue to develop at very rapid rates throughout early childhood. Moreover, the Cravioto and Robles study (*16*) did not follow up the children in later childhood to evaluate later aspects of development, and their conclusions cannot be extended for outcomes beyond the immediate recovery period.

Though animal experimental data have indicated that particular vulnerabilities to nutritional stress exist in brain in relation to the age at which the stress is experienced, our knowledge is incomplete. We cannot now identify with certainty a specific age after which such vulnerability ceases to exist. Since many aspects of neuronal growth and differentiation continue to occur throughout the first years of life (*28, 29*), however, it is unlikely that vulnerability is restricted to the prenatal period and early infancy.

Subjects and Study Design

The 74 severely malnourished children (hereafter referred to as index patients) were all boys who had been hospitalized for treatment of severe infantile malnutrition during the first two years of life. Sixty of these children had been inpatients on the metabolic ward of the Tropical Metabolism Research Unit of the British Medical Research Council, Mona, Jamaica, W. I. The remaining 14 patients were added to have fuller representation over the entire first two years of life. The latter were obtained from the pediatrics ward of the University Hospital, University of the West Indies, Mona. At the time of hospitalization all the children were suffering from severe malnutrition, reflected variously in syndromes of marasmus, kwashiorkor, or marasmic kwashiorkor. Detailed clinical and metabolic records were available in all cases. The children received an average of eight weeks of inpatient care. In general, follow-up visits in the homes were conducted for two years following discharge.

Sixty-four male infants had been treated in the metabolic ward of the Tropical Metabolism Research Unit in the years relevant to the study. At follow-up two of these children and their families had moved and could not be

traced. Two additional children were found but not included in the study, one because he was a mongoloid and the other because of the presence of infantile hemiplegia, most probably of perinatal origin. The remaining 60 children were all included in the follow-up study. The 14 patients from the pediatrics ward were the first 14 to be located from an initial pool of 50 patients. Approximately half of them lived in the city of Kingston, and the remainder lived in other towns, villages, and rural districts, some of which were more than 160 km from Kingston.

At the time of the study the index patients were 5 years 11 months through 11 years old. These ages were selected in order to be far enough removed from the time of acute illness to eliminate the effects of immediate sequelae and for the children to be at an age at which intelligence testing has predictive validity for later life.

Whenever there was a male sibling of the index patient between six and 12 years of age and nearest in age to the index patient, and without a history of severe clinical malnutrition, he was included in the study. Because of widely varying patterns of family composition in Jamaica, a sib was defined as a child having the same biologic mother as the index patient and having shared a home residence with the index child for most of his life. Thirty-eight such sibs were available and studied. Because of the selection criteria used, the sibs were somewhat older than the index patients.

In addition to the sibs, a classmate or neighbor comparison was selected for each index patient and for each sib. For index children and sibs attending school, two classmates of the same sex closest in age to the index patient and the sib were selected. On evaluation, if the first comparison child was not available for examination, the second comparison was used. Some of the index boys and sibs, though of school age, were not going to school. In such instances, a comparison case was chosen by finding the nearest neighboring child who was not a relative and who was within six months of the index patient's age. For some index patients at small schools no classmate was within six months of age. Then neighbor children were also used as comparisons. In three cases comparison children could not be brought in for study. This resulted in 71 matched pairs of index and comparison children. Table 1 summarizes the ages at testing of the children studied. The comparison group should not be considered as controls but rather as children who were identified because of their geographic proximity and their closeness in age to the index children.

Detailed interviews were conducted to secure the background histories of all children. These indicated that eight of the comparison children had been sick between the ages of one month and two years, either from malnutrition or with symptoms that could have been associated with malnutrition. Only one of them was hospitalized during that age interval, for two weeks because of diarrhea and vomiting.

At the time of follow-up these data were obtained about each of the boys in the study to assess their current physique and level of functioning: (1) height, weight, and head circumference; (2) a detailed assessment of pediatric neurologic status; (3) intelligence level using the WISC and the verbal portion of the WPPSI; (4) estimates of intersensory development, perception, laterality, lateral aware-

Table 1. Ages of index, sib, and comparison boys at time of IQ testing.

Age in years/months	Number of		
	Index	Sib	Comparison
5-0 to 5-11	1	—	5
6-0 to 6-11	19	3	16
7-0 to 7-11	16	6	14
8-0 to 8-11	15	10	13
9-0 to 9-11	19	4	20
10-0 to 10-11	4	9	3
11-0 to 11-11	—	4	—
12-0 to 12-11	—	2	—
Total	74	38	71

ness, and motor coordination; (5) an estimate of educational achievement using the Wide Range Achievement Test; (6) teachers' assessments of school performance and behavior in the school setting; (7) sociometric data to obtain a measure of the child's social acceptability by his peers, and (8) mothers' assessments of behavior at home.

To obtain a detailed social and biologic history of each subject and information about the general ecologic conditions that might influence the children's development, a detailed interview was conducted with each boy's mother or guardian.

Results

Thus far, the major focus of analysis has been directed toward determining whether the index children show impairment in physique and functional development compared with the other boys studied.

The characteristics of the groups selected would lead us to anticipate that the index patients who suffered acute malnutrition would be most severely impaired, that their sibs, some of whom would have experienced chronic subnutrition but not an acute severe episode, would have been intermediately impaired, and that comparison children, who did not belong to a family having a child with a history of severe clinical malnutrition, would be least impaired. The findings bear out these expectation, but they will only be summarized here because they are to be reported in detail elsewhere.[1]

[1] Hertzig, M. E., et al. Intellectual levels of school children severely malnourished during the first two years of life. *Pediatrics*, 49:814–24, 1972.

Richardson, S. A., et al. The behavior of children in school who were severely malnourished in the first two years of life. *J Health Soc Behav* 13:276–84, 1972.

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Physical attainments

Index boys were significantly shorter in height, weight, and head circumference than their classmate or yardmate comparisons. Index boys were significantly lighter and had smaller head circumferences for age than their sibs, but were not significantly shorter. The sibs did not differ from their classmate or yardmate comparisons in either height or weight.

To determine whether physical growth recovery of the index boys might be different in different environments, boys who had grown up in urban and rural surroundings were compared. It was found that index-sib differences held for rural but not for urban environments.

Intellectual functioning

All IQ measurements were significantly lower for the index boys. For the Full Scale, Verbal, and Performance IQ measures the index patients have the lowest mean scores, the sibs occupy an intermediate position, and the comparison children have the highest scores. These differences are in accordance with expectation. The three IQ measures are seven to nine points lower for the index children than for the comparisons. Each of the differences is statistically significant at less than the 0.001 level of confidence.

That these mean differences in IQ score are not the result of a few cases of extreme competence in the comparison group or of extreme incompetence in the index patients but represent differences over the whole range is clearly indicated in Figure 1. As may be seen from this figure, the groups, in general, differed from one another in Full Scale IQs over the whole range of measures. The cumulative frequency percentage curves for Performance and Verbal IQs in the two groups are almost identical in form, and indicate that the comparison group is also superior on these measures.

The index children also have lower scores on the three IQ measures than their sibs. The Full Scale and Verbal IQ differences are statis-

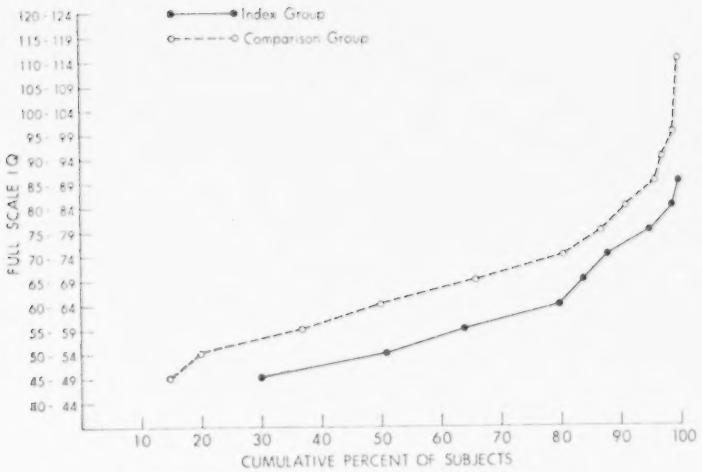

Figure 1. IQ distribution of index and comparison patients.

tically significant ($p < 0.025$). Differences in Performance IQ are not significant. When the sibs are contrasted with the comparison children, they are found to differ from them significantly only in Performance IQ.

Before the results can be interpreted, two further analyses are required. In the first place sibs tend to be older than index and comparison subjects, and the differences between the sibs and the other two groups could have derived from this age difference. Moreover, since ordinal position can affect IQ within a sibship, differences between sibs and index patients could have been the result of differences in ordinal position. To deal with the first question, the relation of IQ level to age was analyzed in each of the groups. No age trends for IQ were found. To deal with the second question, older sibs were separately compared with younger index patients and younger sibs with older index patients. Identical trends and directions of difference were found when the sibs were respectively in lower or higher ordinal positions in the sibships. These analyses indicate clearly that the differences among groups were not artifacts either of age or of ordinal position.

School achievement

In the reading, spelling, and arithmetic tests of the Wide Range Achievement Test, the index boys were on average 7 to 9 points lower in their quotients than their classmate comparisons. In the same three tests the sibs were on average 4 to 9 points lower than their classmate comparisons. The index and sib average quotients on the three tests were almost identical in each case, being less than one point apart. Index children had significantly lower scores than their classmate comparisons on all three tests. Sibs were significantly lower than their comparisons on reading ($p < 0.05$ one-tail), but the differences on the spelling and arithmetic tests were only trends.

Teachers' evaluations represent judgments of functioning based on continuing contact with the child in a school setting. Such judgments provide a different perspective than that derived from an achievement test. Because teachers cannot be expected to have uniform standards for evaluating children, comparisons were made only between pairs of children judged by the same teacher. On the overall evaluation of school performance, the teachers' rating for the index boys were lower than their classroom

comparisons ($p < 0.005$). Twenty-four per cent of the index children were rated in the lowest category of quality of overall school work—"He is severely backward"—compared with 8 per cent of the index comparison children. No significant differences were found between sibs and their comparisons.

Behavior in the school setting

Index boys were judged by their teachers to have worse attention and memory, and to be more easily distracted and less spontaneous and contributive in classroom discussion than classmate comparisons. In their social relations the index children get along less well with their peers and are less cooperative with their teachers. They had more frequent problems in classwork and more often manifested behavior and conduct problems. When sibs were compared with their classmates, the only behavioral difference found was greater distractibility in the sibs.

Age of severe malnutrition

The age distribution of the index children when they were hospitalized for the treatment of severe malnutrition ranged from three to 24 months, with admissions at almost every month between these ages.

If the age at which a child is hospitalized for severe malnutrition is systematically related to the severity of his physical and functional impairment, we would expect a significant positive correlation to exist between age at admission and attributes at school age. When physical growth, IQ, and school achievements and behavior are correlated with age at hospitalization, there is no significant association with earliness of illness. The data indicate a random relationship between the age of the severely malnourished child at hospitalization and function or growth attainments at school age.

Because the replication of cells in the central nervous system tends to be completed before the age of nine months, it has been suggested that children experiencing severe malnutrition before that age are at particular risk of brain damage and lowered intellectual level. We therefore considered it desirable to compare those children who had been hospitalized before the age of eight months with those admitted to hospital for severe malnutrition at later ages. When children admitted before eight months of age, between eight and 12 months, and between 13 and 24 months are compared, no significant differences are found among groups for Full Scale, Verbal, and Performance IQ, growth attainment, school achievement, or school behavior. The data thus provide no support for the hypothesis that systematic differences in outcome at school age are attributable to severe malnutrition at different ages during the first two years of life.

The second aspect of the study deals with the ecology of growth and functional development of these children. In this approach nutritional history is considered as one variable in the context of the wide range of influences that affect the development of children. This strategy is described in part in the paper by S. A. Richardson in this monograph.

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ENVIRONMENTAL CORRELATES OF SEVERE CLINICAL MALNUTRITION AND LANGUAGE DEVELOPMENT IN SURVIVORS FROM KWASHIORKOR OR MARASMUS[1]

Joaquín Cravioto and Elsa DeLicardie[2]

At the community level, malnutrition, or more specifically protein-calorie malnutrition, is a man-made disorder characteristic of the poorer segments of society, particularly in pre-industrial societies. In the latter the social system consciously or unconsciously creates malnourished individuals, generation after generation, through a series of social mechanisms that includes limited access to goods and services, limited social mobility, and restricted experiential opportunities at crucial points in life.

When applied to an individual, the term "protein-calorie malnutrition" is a generic name used to group the whole range of mild to severe clinical and biochemical signs present in children as a consequence of a deficient intake or utilization of foods of animal origin, accompanied by variable intakes of rich carbohydrate foods. Kwashiorkor and marasmus are the names given in the U.S. and Commonwealth literature to the two extreme clinical varieties of the syndrome that occur in infants and children. The appearance of marasmus or kwashiorkor is related to the age of the child, the time of full weaning, the time of introduction of food supplements to breast milk, the caloric density and protein concentration of the supplements the child actually ingests, and to the frequency and severity of infectious diseases present during weaning.

Research in the field of malnutrition has recently centered on the question of the later functioning of individuals who suffered from it in early life. A series of studies done in various parts of the world have shown that survivors of early severe malnutrition differ from well-nourished children in a great variety of functional ways ranging from psychomotor behavior to intersensory organization (*2, 4, 5, 6, 7, 10, 12, 13, 15, 16, 17, 18*). The problem now is to separate the specific role that the deficient food intake may have from the contribution of other factors that interfere with the correct functioning of the individual. The reason for this rests on the fact that malnutrition in humans is an ecologic outcome (*11*), with many of the factors that either cause or accompany malnutrition being in themselves capable of negatively influencing mental and behavioral development. It is obvious that this type of research question can only be approached through the longitudinal observation of children at risk of appropriate controls. With this idea in mind, we have been engaged

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since March 1966 in an ecologic study of a cohort of children born in a community where preschool malnutrition is highly prevalent, and where other factors related to the life of the children have variations of sufficient range to permit associative analyses to be carried out.

In brief, the project is the study of a total one-year cohort of children, all born in a rural village between March 1, 1966, and February 28, 1967. The children and their families have been closely observed from the nutritional, pediatric, socioeconomic, and developmental points of view in a coordinated manner, with great attention to detail, and so far as feasible using validated research instruments. A good number of the instruments were devised and tested by the project staff during the 10 years before the start of the cohort's induction.

The objective of the study is to analyze the relationship between the conditions surrounding care of the child, especially as they affect his nutrition, and the course of his physical growth, mental development, and learning.

The main hypothesis to be tested is that intellectual growth at all stages and school-age performance are related to the nutritional and health conditions to which the child had been exposed.

The children first brought into the study during the prenatal period have been followed for five years and will continue to be observed until they have completed their first seven years (March 1974), the earliest time at which certain crucial mental examinations can be meaningfully applied. At that time the children can all be assessed in the relatively uniform environment of a primary school.

While the particular focus of the project is on the relationship between nutrition and mental development, by the nature of both variables the design is that of an ecologic study of young children in their family and social environments.

The ecologic approach was chosen because it constitutes a particular form of the natural history method, which seeks to determine the nature of effective variables through a consideration of their interrelations in a single population. When applied to the problem of malnutrition, it attempts to determine patterns of cause and consequence by considering the interrelations among nutritional, health, and social factors. Moreover, by orienting itself longitudinally the ecologic approach can identify age-specific conditions at risk, relate antecedents to consequences at different developmental stages, and integrate biologic and social time scales. It can take into account both the general and the microenvironment of the developing individual and deal with the interaction of biologic and social variables. Perhaps most important for its usefulness is the fact that it employs uncontrolled variation as the fact of study. A basic requirement for the use of the ecologic method is, therefore, sufficient variation in the attributes to be considered in the population studied. If such variation is present, associative analysis can identify, segregate, and interrelate the factors influential in affecting the consequences with which one is concerned.

Through the use of the ecologic method we plan to analyze: (1) the influence of social, economic, and familial conditions on the development of malnutrition; (2) the effect of malnutrition on physical growth, mental development, and learning, and (3) the interaction of nutritional factors with infectious disease, family circumstances, and social circumstances on the processes of growth and development.

The intensive analysis to be done can be understood only through a detailed acquaintance with the setting of the study, the cohort under observation, and the measures used.

The Setting of the Study

To examine the complex set of variables with which our investigation is concerned, we have had to study a large group of children. Estimates of sample needs required the selection of a community of sufficient size to provide at least 250 births in the annual cohort to be fol-

lowed longitudinally. The community chosen also had to contain a considerable range of social and nutritional conditions as well as be one in which the population was likely to be cooperative, willing to enroll, and remain in the study. For a longitudinal study, it was clearly essential that the population be relatively stable and that a high proportion of the families and infants enrolled at birth for study be likely to continue to live in the community for the duration of the inquiry period.

The community chosen met these requirements. Selection was based on previous experience with rural communities and field studies. In one of these studies the present village was a participating community and had shown a high level of population stability over time, excellent cooperation, and a wide range of variation in social, economic, familial, and health attributes. Furthermore, its annual birth expectancy was 300.

The village is located in a semitropical, subhumid zone in southwestern Mexico in a primarily agricultural region where arid hillsides alternate with fertile valleys and meadows. It is at an altitude of between 900 and 950 m above sea level and has a hot, subtropical climate modified by its altitude. The median annual temperature is between 23° and 25°C in the shade, and the climate ranges from chilly winters to very hot summers in which daily high temperatures of 40°C are common. A small river whose waters are used for irrigation, laundering, and other general purposes runs through the village.

As is characteristic of Mexican rural villages in this region, the town radiates outward from a shaded central plaza along a series of unpaved and rutted dirt streets, which are related to one another to form roughly quadrangular blocks. A street map of the village is presented in Figure 1. The small inset at the upper right indicates the arrangement of households within two specific blocks.

The area surrounding the townsite was entirely agricultural, with sugar cane constituting the major commercial crop. Small amounts of cotton and rice were also grown commercially.

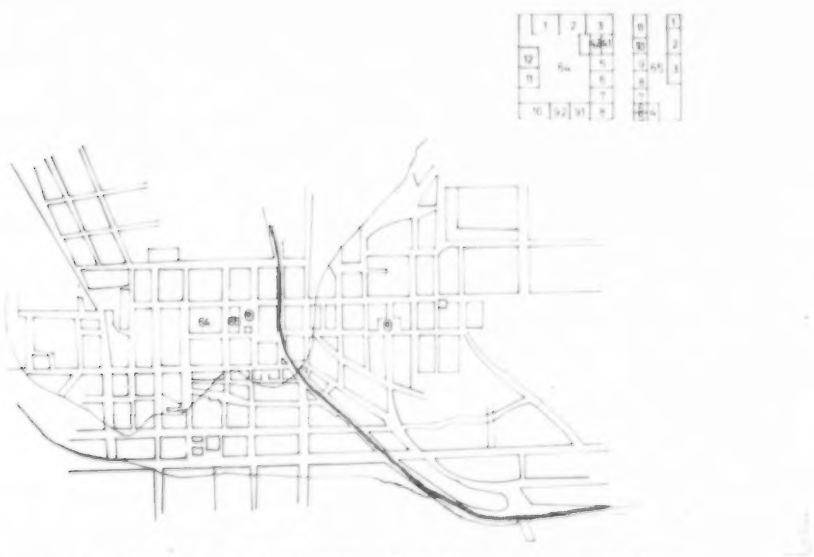

Figure 1. Plan of study village; inset at upper right shows arrangement of households in two specific blocks.

Interspersed among the large commercially organized fields were small family parcels and rentable areas that the villagers used for the production of food crops—principally corn, chilis, tomatoes, and other garden crops and fruits—for their own consumption.

In 1965 we carried out a census of all village households. Our findings indicated the presence of 5,637 persons from 0 through 85 years of age, organized in 1,041 families. The numbers of men and women were insignificantly different: 2,830 men and 2,807 women. The distribution by age and sex in the population are presented in Figures 2 and 3. As may be seen from both figures, the population was relatively young: fully 50 per cent of the inhabitants were under 15 years of age, and 80 per cent were under 35. In a stable community such as this, these age ratios naturally reflect a reduced life expectancy calculated from birth. No notable sex differences in age-specific frequency were found.

Birth rates over the previous 20 years had been at a mean of approximately 55 per thousand and led to an annual expectancy of approximately 300. In the 12-month series of births upon which the current study is based, the predicted expectation was fulfilled.

The principal occupation of the villagers was agriculture, although relatively small numbers of people were employed as workers and artisans, and a still smaller number were engaged in commerce or in the practice of a profession. The occupations, as reflected by the main sources of family income, are presented in Figure 4. Approximately 65 per cent of the population gained its livelihood directly from agriculture; 12.5 per cent worked at a variety of jobs, including transport work, labor in the small cotton gin or mattress factory, carpentry, masonry, or other skilled and semiskilled crafts; and 9 per cent were small tradesmen, shopkeepers, or teachers. Included in the last group were one architect, one engineer, and two

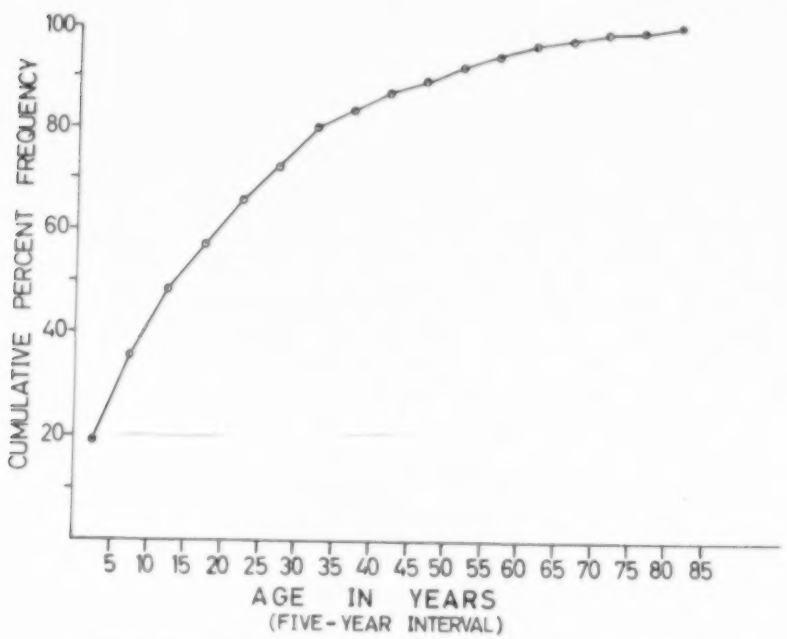

Figure 2. Cumulative percentage of village's population distribution by age.

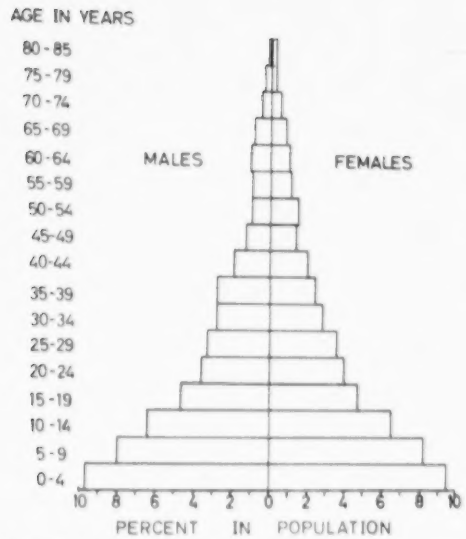

Figure 3. Age pyramid by sex.

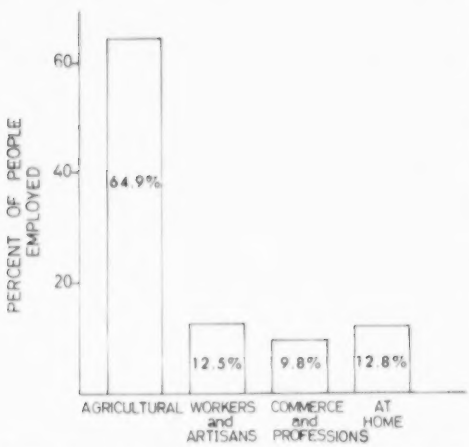

Figure 4. Main sources of family income in village. "At home" families are those in which mothers and children were mainly dependent on some other familial or social source of support.

physicians who served both the village proper and the surrounding communities.

The social and economic status of people who worked in agriculture is by no means homogeneous, as can be seen in Figure 5. Most workers were agricultural day laborers (*jornaleros*), whose employment is seasonal and whose income is marginal. They supplemented their income by the seasonal planting of food crops on communal lands at some distance from the village. A second group comprising some 23 per cent of those engaged in agriculture had family plots that are cultivated for both small-scale commerce and self-use. The best-situated cultivators were either small owners or renters of relatively high-grade farmlands; taken together, these two groups constituted approximately 7 per cent of those who drew the main source of their family income directly from agriculture.

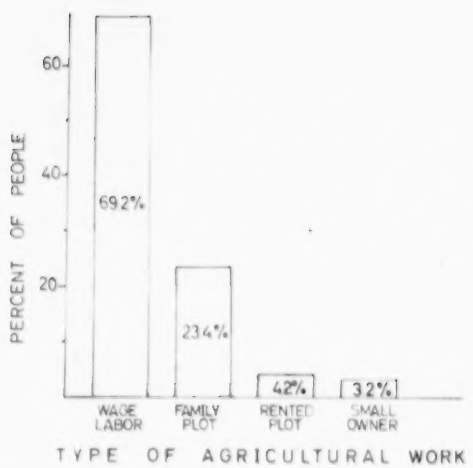

Figure 5. Percentages of people engaged in different types of agricultural work.

A few words are required to describe the different types of land-holding if the different kinds of agricultural work are to be understood. The *jornalero* owns no land and works entirely for wages. He is, in the main, not insured for social and health services and represents the most economically deprived and unstable segment of the population. He may be described as an agricultural proletarian.

The ownership of land by individuals is of two kinds, the first of which is the family plot (*ejido*). These are small parcels of land, ranging generally from 0.5 to 1.25 hectares, that

were distributed to landless peasants (*peones*) at the time of the agrarian reform (1917). Such land is held by the family in perpetuity so long as it is worked, but it may not be sold, traded, divided, or attached for debt. All the *ejidos* owned by the villagers had been amalgamated into a sugar cooperative. The second type of individual land ownership is represented by the small proprietors whose plots are generally larger than the *ejidos*. Their plots may be bartered, sold, mortgaged, attached for debt as private property, and divided or sold with no special limitations. The rented lands are generally larger, and those who operate them are economically better off than the other agricultural groups.

Until 30 years ago the village was almost totally agricultural in character. Since then it has been in a state of slow transition to a mixed economy representing more advanced levels of both industrial technology and agricultural organization. The beginning of the transition was marked by a national law authorizing and facilitating the development of agricultural combines and cooperatives. Shortly after this law was enacted, a large cane-growing cooperative and a sugar refinery 17 km from the village were established. Much of the land surrounding the village was assimilated into this large cooperative. A mattress factory employing 20 workers was established 12 years ago, and this was followed five years later by the construction and operation of a small cotton gin.

These economic changes have been accompanied by greater availability of transportation, the improvement and construction of roads, and a considerable increase in interaction between people in the village and more advanced urban and semiurban centers. The technologic advances have been accompanied, too, by the improvement of a variety of village services including school, a central water supply, and a social welfare and health center. The village now has one kindergarten, two primary schools, and one school accepting pupils to the ninth grade. Attendance at school is compulsory starting at seven years of age and continuing for six years; beyond this, study may be voluntarily continued for three more years inside the village and on higher levels outside it.

Variation in health conditions in the community and in the relative opportunities available for the growth and development of children are reflected in two sets of data. The first of these deals with the weights and heights of school children. A comparison of the growth attainment of children attending school in 1965 with the growth of children who were at school a generation earlier suggests that the technologic changes were not accompanied by either a change in mean height or weight for age or any diminution in the variability of these characteristics in the population. The Wetzel Grids presented in Figure 6 illustrate this lack of change.

The second set of data uses tuberculin reactivity as an index of health risk. It reflects the high frequency of the children's exposure to sources of infection. Age-specific values for positive reaction to tuberculin show a continuing rise of positive reactors with age, as can be seen in Table 1.

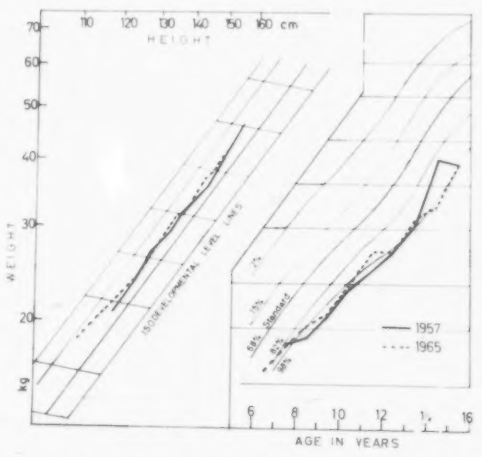

Figure 6. Relation between height and weight in two generations of school children.

Table 1. Distribution by age of positive PPD reactors among village children.

Age (years)	Positive reactors (%)
3	0
4	0
5	3.7
6	2.1
7	7.8
8	12.4
9	8.7
10	7.6
11	12.3
12	12.6
13	16.1
14	15.9
15	20.0
16	37.5
Average	11.2

As a final step in assessing the suitability of the village for our purposes, we made a sampling survey of households with children of preschool age for clinical evaluation of children and the assessment of the incidence of subnutrition as indicated by a depression of weight for age (Table 2).

The figures indicate that at all levels in the preschool period, mild, moderate, and severe degrees of malnutrition were present in the community, with a frequency that made it fairly representative of communities in which chronic subnutrition is prevalent. All the data considered provided a basis for choosing the community as a suitable site in which to conduct a longitudinal study of the ecology of growth and development in a total annual cohort of births over the preschool and school years.

Table 2. Nutritional status of preschool children in village.

Age (months)	No. of children	Malnutrition (%)		Normal (%)
		Third Degree	Mild-Moderate	
0-5	132	0	5	95
6-11	112	3	9	88
12-23	210	5	18	77
24-35	207	9	21	70
36-47	212	8	8	84
48-59	201	5	11	84

The Birth Cohort

The children

Of the 300 infants born during the 12-month period in which the cohort of births was collected, there were equal numbers of boys and girls. The social origins of these children closely matched the distribution of principal sources of income and occupation in the village as a whole. Minor differences from the overall distribution may be attributed wholly to the constriction in age range associated with reproduction.

The manner in which principal sources of family income were represented in the cohort are presented in Figure 7. The great majority of families were agricultural, and 66 per cent of all children were from such families. Sixteen per cent of the children were born to families of workers or artisans, with four times as many of the former type of family represented as of the latter. Equal numbers of tradesmen and professional families were present in the 4.6 per cent of the births among these social

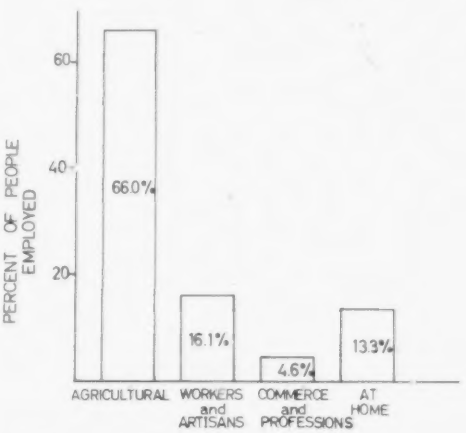

Figure 7. Main sources of family income in the cohort. "At home" families are those in which mothers and children were mainly dependent on some other familial or social source of support.

groups. Some 13 per cent of the births occurred in families in which it was difficult or impossible to define an intrafamilial source of income. These families were ones in which the mother and children were in the main dependent upon some other familial or social source of support; they are labeled *at home* in Figure 7.

The distribution of birth weights in the annual cohort is presented in Figure 8. Among the 291 infants who lived long enough to be weighed, there were eight weighing 1,500 to 1,999 g, 28 weighing 2,000 to 2,499 g, 147 weighing 2,500 to 2,999 g, 86 weighing 3,000 to 3,499 g, and 22 weighing 3,500 to 3,999 g. Mean birth weight was 2,898 ± 444 g. A birth weight of less than 2,500 g was thus obtained for 12.3 per cent of the cohort, whereas only 7.6 per cent of the children weighed more than 3,500 g. As would have been expected from other bodies of data, the mean birth weight of boys was significantly higher than that of girls (Figure 9). The mean birth weight of boys was 2,977 ± 394 g and that of girls 2,860 ± 408 g. The mean difference of 117 g was significant at the 0.02 level of confidence.

The distribution of total body length at birth for the children in the cohort is presented in Figure 10. The median body length was 48.5 cm, with 25 per cent of the children

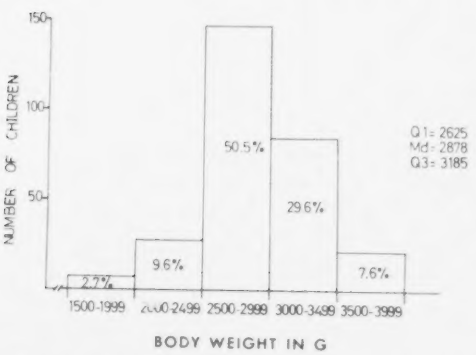

Figure 8. Birth weight of children in annual cohort of births.

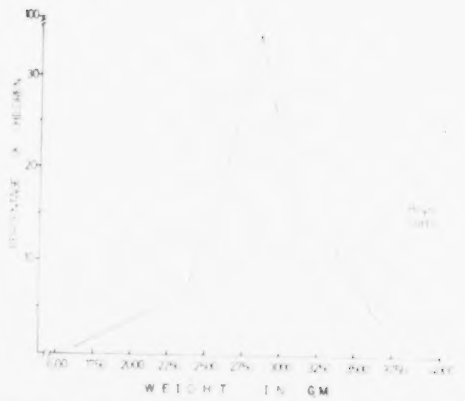

Figure 9. Sex distribution of body weight at birth.

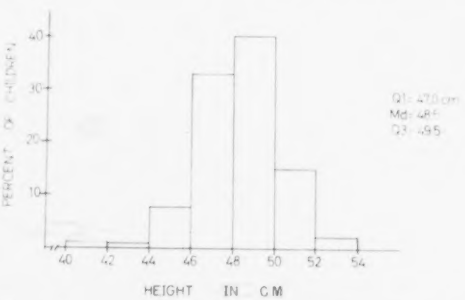

Figure 10. Distribution of total body length in cohort at birth.

having a body length of less than 47 cm and an equal number having body lengths between 49.5 and 53 cm. As was the case for birth weight, mean body length at birth was significantly higher in boys than in girls. As may be seen from Figure 11, boys had a mean length of 48.7 ± 1.8 cm and girls one of 48.0 ± 2.0 cm. This difference, though small absolutely, is statistically significant ($t = 3.3$; $p < 0.1\%$).

Mortality and emigration

Of the 300 children delivered, 296 were alive at birth and four were dead at delivery. The stillborn were born into no particular occupational group: one child was born to a family whose principal source of income was agricultural day-labor, one to a cultivator of

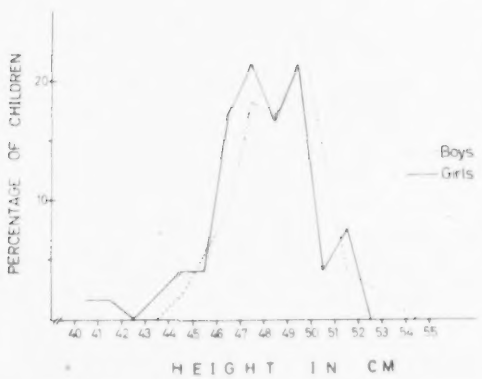

Figure 11. Distribution of body length at birth by sex.

rented lands, and two others to owners of family plots. Of the 296 live-born infants, seven died during the first week of life (23.5 per 1,000) and three others during the remainder of the first month. If the stillborns and those who died during the first week of life are combined and considered as perinatal deaths, the rate for such deaths is 36.6 per thousand. Combining all deaths of live-born infants during the first month results in a neonatal death rate of 33.6 per thousand.

In the main, the infants who were stillborn or who died during the first month of life were of low birth weight. Because of custom, unfortunately, those who were stillborn or who died a few hours after birth could not be weighed. The remaining seven children had birth weights below 2,300 g.

Nine infants died during the remainder of the first year of life, seven between the second and sixth months of life. It is of interest that one of the two infants whose death occurred after six months of life was mortally bitten by a scorpion. Taken as a whole, these data indicate that 19 live-born infants in the cohort died in the first year of life, with a resultant infant mortality rate of 63.3 per thousand.

The children who died were not randomly distributed in the cohort with respect to weight or body length at birth. The mean birth weight in the cohort was 2,898 g, and the mean birth weight of the children who died during the first year of life was 2,536 g. Similarly, mean body length of the deceased was 45.8 cm, as contrasted to a mean body length of almost 49 cm in the cohort as a whole. Both of these mean differences were significant at less than the 0.01 level of confidence. It was of course possible that these mean differences were contributed by an excess of premature infants among the infants who were stillborn or who died in the first year of life. Such a possibility is supported by the fact that six of the infants who died were prematures. That number results in a prematurity of 260 per thousand deliveries, which is more than twice the rate of 124 per thousand deliveries present or in the cohort as a whole. If one considers only infants above 2,500 g at birth among the stillborn and infant deaths, however, one still notes a preponderance of poorly developed children, with 63 per cent of them having birth weights below the median of the cohort and the remainder with weights only slightly higher than the median birth weight. Only three of the 23 infants had body lengths equal to or greater than the median of the cohort as a whole. Two were exactly at the median and one was 1 cm higher. All other infants were between 1.5 and 7.0 cm shorter than the median body length for the whole cohort. It appears, therefore, that those who were either stillborn or who died during the first year of life were less well developed in utero than the survivors.

After the cohort's first year of life 10 more children died. With the exception of two children whose deaths were due to accidents (severe extensive burns, and bronchoaspiration) and a child who died of hypoprothrombinemia and purpura, all other deaths in this age period can be directly related to infectious disease accompanied in most cases by severe malnutrition.

Table 3 shows the sex, age, and probable cause of each death that occurred during the cohort's first five years.

Besides the 300 children born in the village during the calendar year 1966-67, twelve fami-

Table 3. Mortality in cohort during first five years of study.

Period	Number	Code	Sex	Age at death (days)	Cause of death
Still-born	1	13.12	M	0	unknown
	2	13.5	F	0	unknown
	3	13.26	M	0	unknown
	4	4.22	F	0	unknown
First week of life	1	12.24	F	1 hour	unknown
	2	13.28	F	1 hour	unknown
	3	7.12	F	5 hours	bronchoaspiration
	4	9.18	M	5 hours	prematurity
	5	6.11	M	6 hours	hyaline membrane
	6	8.24	M	2 days	congenital malformations and bronchopneumonia
	7	13.2	M	3 days	bronchopneumonia
Days 8-30	1	4.23	F	9	ABO incompatibility
	2	2.3	F	17	electrolyte disturbance
	3	12.15	F	21	prematurity
Days 30-360	1	13.29	M	40	electrolyte disturbance due to diarrhea
	2	13.16	M	43	pyelonephritis
	3	12.14	F	76	electrolyte disturbance due to diarrhea
	4	10.13	F	78	septicemia
	5	11.2	F	85	bronchopneumonia
	6	11.27	F	130	electrolyte disturbance due to diarrhea
	7	12.17	F	139	electrolyte disturbance due to diarrhea
	8	7.11	F	268	scorpion bite
	9	5.24	M	312	electrolyte disturbance due to diarrhea
One to five years	1	3.22	M	375	electrolyte disturbance due to diarrhea
	2	13.6	F	400	bronchopneumonia and malnutrition
	3	1.31	M	405	bronchoaspiration
	4	11.6	F	435	bronchopneumonia and malnutrition
	5	4.19	M	654	acute miliary tuberculosis
	6	2.22	F	737	kwashiorkor amebiasis
	7	11.20	M	1036	kwashiorkor diarrhea
	8	3.1	M	1229	electrolyte disturbance due to diarrhea
	9	9.13	M	1240	third-degree burns
	10	8.22	F	1413	kwashiorkor, purpura

lies came to live in the village during the time of induction of the birth cohort. These families had children less than one year old, and they were included in the longitudinal study.

In the course of the last five years a total of 50 families have left the village. Reasons for emigration are mainly related to better working conditions in another, larger town or Mexico City itself. Table 4 shows the time spent by the children in the study.

As may be seen from the cumulative frequency figures, all 50 children who left the village were examined at least during the newborn period. We have data about the first three months of life for 44, about the first six months for 34, about the first year for 22, about the first two years for seven, and about the first three years for two. Family data were available for all 50 children who emigrated.

Familial and social background

Broadly considered, background factors in the cohort were of three kinds: first, the mother as a biologic and social organism; second, the family structure; and third, objective circumstances of life such as sources of family income and the family's housing conditions. Each kind of factor will be considered in turn, with the

Table 4. Time spent in study by children whose families emigrated from village.

Days under observation	Number of children	Cumulative frequency
0	0	
1-3	0	
4-15	1	50
16-30	1	49
31-90	4	48
91-180	10	44
181-270	7	34
271-360	5	27
361-420	5	22
421-540	3	17
541-610	4	14
611-720	3	10
721-810	1	7
811-900	2	6
901-990	1	4
991-1080	1	3
1081-1170	0	0
1171-1260	1	2
1261-1350	0	1
1351-1440	1	1

exception of sources of income, which has already been discussed.

We shall begin our consideration of the background characteristics of the children by viewing some features of the mother as a biologic organism—her age, height, weight, and previous pregnancies. The age distribution of mothers in the cohort is presented in Figure 12. Ages ranged over 30 years: the mothers included two girls who had their first children at age 13, and one woman who had a child at age 43. The mean age was 25.6 ± 6.8 years, and the median age was 24 years, with 75 per cent of mothers under 30 years of age. The distribution of maternal age tends toward bimodality and, as a whole, contains sufficient variability to permit associative analysis.

The heights and weights of the mothers also varied widely (Figures 13 and 14). The mothers' heights ranged from 133 to 165 cm, with a mean value of 148.2 ± 2.8 cm. The heights were relatively normally distributed, with a slight tendency toward increased frequency in the lower range of stature. The median value was 147.5 cm, and 75 per cent of the women were less than 153 cm tall.

Weight of the mothers ranged from 32 to 86 kg. This upper weight value was markedly atypical and is so indicated by a break in the distribution of values on the x axis of Figure 14. Mean weight was 53.0 ± 4.8 kg with a median value of 51 kg, suggesting a slight

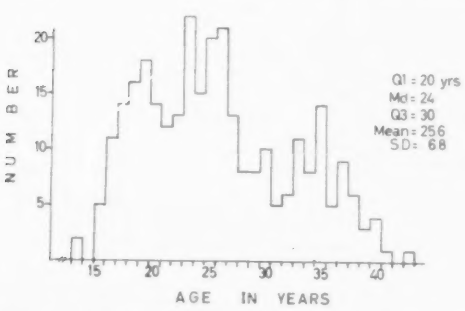

Figure 12. Age distribution of mothers in cohort.

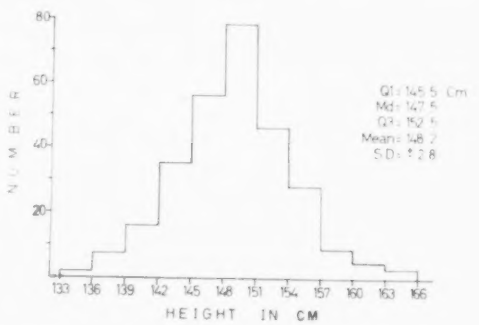

Figure 13. Height distribution of mothers in cohort.

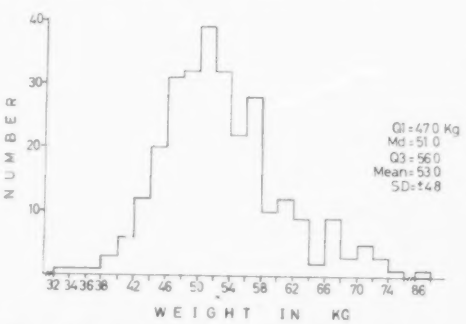

Figure 14. Weight of mothers in cohort.

excess in frequencies at the lower end of the distribution. Both height and weight exhibit sufficient variability to make associative analysis feasible.

The distribution of pregnancy numbers in the cohort is presented in Figure 15. Pregnancy number ranged from one to more than 11, with the highest being 16. Relatively equal numbers of births occurred at pregnancy numbers one through four. Higher pregnancy numbers in the cohort tended to occur with diminishing frequency. From the viewpoint of epidemiologic evidence in obstetrics, it is not meaningful to consider the distribution of parities in terms of mean value. Available evidence suggests that special conditions of risk attend first births and births that occur after the fifth pregnancy; enough cases in each of these parity ranges exist to permit analysis within the cohort of births.

In addition to the foregoing biologic characteristics of the mothers, at least three other characteristics—the mothers' personal hygiene, literacy and educational level, and contact with information mass media—may be considered in relation to the child's condition at birth. Ratings of personal hygiene ranged from a low of 20 per cent to a high of 100 per cent (Figure 16). The median score was 56.6 per cent, with three-fourths of the mothers scoring below an estimated cleanliness level of 76 per cent. Wide variation in personal cleanliness existed among the mothers, and personal hygiene subgroups could readily be defined.

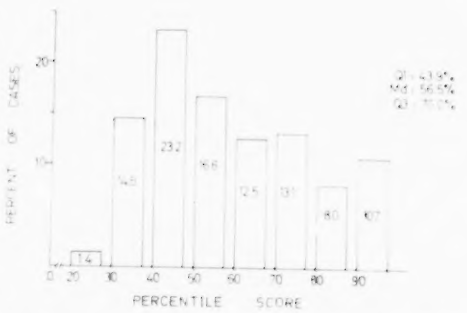

Figure 16. Personal hygiene of mothers in cohort (based on 289 cases).

The mothers' literacy and school attainments are presented in Figure 17. Almost half the mothers were completely illiterate. Another 10 per cent had either become literate through adult literacy campaigns or acquired basic literacy by completing one school grade. Only 6.3 per cent had completed the full primary school curriculum of six years, and the remaining 1.5 per cent had schooling beyond primary school. From a functional point of view it was possible to group the mothers into four classes: (1) the illiterates, (2) the adult literates and those who had completed the first and second grades, (3) those who had completed the third, fourth, or fifth grades, and (4) those who had completed primary school. These

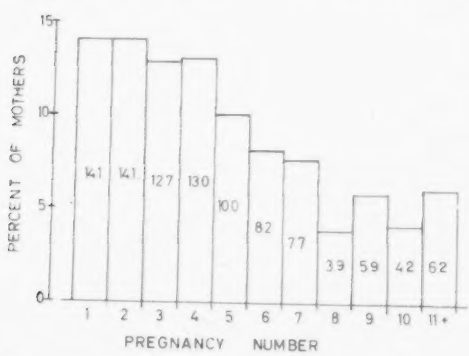

Figure 15. Distribution of pregnancy numbers in cohort.

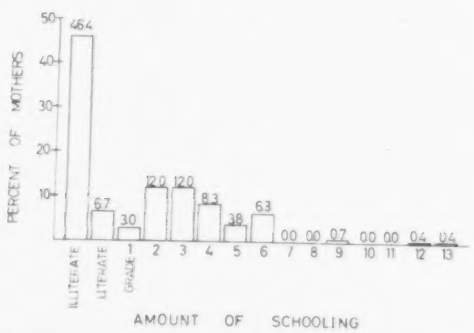

Figure 17. Literacy and school grade completed by mothers in cohort.

functional groupings have been used in later associative analyses.

As may be seen from Figure 18, very few of the women had any exposure to television. Half had little or no regular contact with the radio, and almost 70 per cent read no newspapers except episodically. If consideration of newspaper reading is limited only to the literate segment of the population, slightly fewer than 50 per cent of the mothers actually did so. Thus, in the present study we have viewed radio as the most effective medium of disseminating mass information and have restricted our consideration of the relation between the child's characteristics and the mother's contact with mass media to this medium.

Family size and the sanitary characteristics of the household are presented in Figures 19 and 20, respectively. There was considerable variation in both of these attributes. Family size ranged from a single-child family of three individuals to both nuclear and extended families of a dozen or more members.

The sanitary characteristics of the household varied widely. Most households were substandard, but a considerable number exhibited good to excellent conditions and facilities. Sufficient variation existed to permit the sanitary characteristics of the household to be related, as a differential background factor, to the child's characteristics.

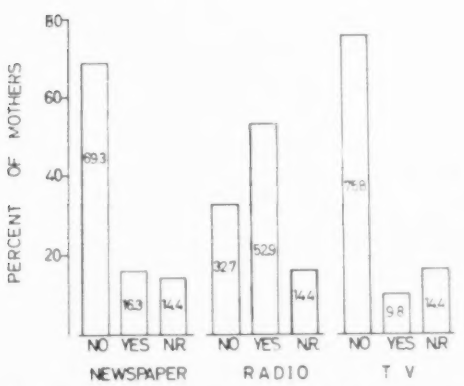

Figure 18. Contact of mothers in cohort with information mass media.

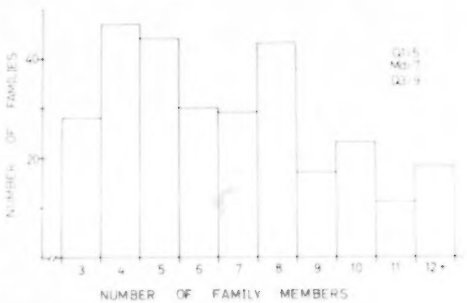

Figure 19. Size of families in cohort.

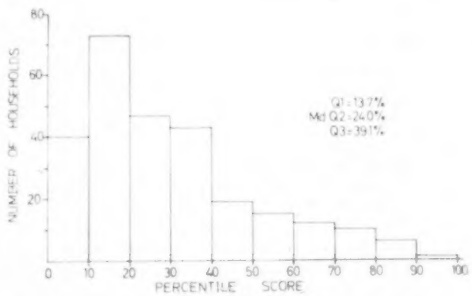

Figure 20. Sanitary characteristics of households in cohort.

The Variables

In the course of the study we have been concerned with two sets of variables: those relating to the child's family circumstances and background environment, and those relating to characteristics of the child himself. We have avoided the terms "antecedent" and "outcome variables," because among each of the general sets of factors certain characteristics may with equal justification be considered as antecedents or consequences of others within the same set. Thus, the mother's education may well affect her patterns of personal hygiene and preferred mode of child care. Similarly, among the variables that characterize the child, a factor such as birth weight may well be an important antecedent for outcomes at later ages.

In general, three types of background factors have been considered: family pattern, biologic and psychosocial characteristics of the parents and caretakers, and macroenvironmental characteristics of the child ranging from survival to physical and behavioral changes with age.

Data for ratings of variables were obtained by interview, by direct observation and measurement, by clinical assessments, and by the application of special tests.

The reliability of all measures and ratings have been assessed, and any measures with excessive intra- or interexaminer, or score-rescore error levels were either improved by modification or eliminated. For somatometric measurements including weight and height, scales were regularly recalibrated and examined. Errors beyond the 2 per cent level were considered excessive. For rating scales, reliability levels expressed as retest or rescore correlation coefficients, or both, of less than 0.82 were considered unacceptable.

The director of the study, the senior psychologist, the senior pediatrician, and the social worker-nutritionist, acting as a research committee, shared the responsibilities of quality control and maintenance of strict standardization and completeness in data collection. The senior biostatistician of the project has been a member of this committee since the time he joined the team.

The types of studies already made of each of the 229 children remaining in the cohort at five years of age (300 births plus 12 arrivals during the first year of study, minus 33 deaths and 50 emigrations), as well as the tests to be given those remaining in the study in their fifth and sixth years, are shown in Table 5:

Table 5. Studies made of children in cohort.

Variable	Measurement	Age period	Frequency
1. Growth			
a. Physical			
	Body weight	0-5 years	fortnightly
	Head, chest, height, and arm circumference	0-3 years	monthly
		3-4 years	bimonthly
		4-5 years	thrice yearly
	Skinfold thickness	0-3 years	monthly
		3-4 years	bimonthly
		4-5 years	thrice yearly
	Bone age	4-5 years	once yearly
b. Mental			
	Psychomotor, adaptive, language, and social-personal development	0-2 years	monthly
		2-3 years	quarterly
		3-4 years	thrice yearly
	Bipolar concept formation	2-3 years	thrice yearly
		3-4 years	twice yearly
		4-5 years	twice yearly
	Finger-thumb opposition	3-5 years	twice yearly
	Finger localization	4-5 years	twice yearly
	Wechsler preschool and primary scale of intelligence	4-5 years	twice yearly
	Styles of response to cognitive demands	4-5 years	twice yearly
	Sensory-motor and movement skills: static balance; dynamic balance; visual-motor coordination involving aiming and accuracy, motor control, and inhibition	4-5 years	twice yearly
	Spontaneous language	5-7 years	twice yearly
	Psycholinguistic abilities: language decoding (meaning); language encoding (expression); grammatical levels of decoding and encoding; development and growth of grammatical language	5-7 years	twice yearly
	Visual perception and form recognition	5-7 years	twice yearly

Table 5. *(cont.)*

Variable	Measurement	Age period	Frequency
	Intersensory integration (visual-haptic, visual-kinesthetic, kinesthetic-haptic, auditory-visual	5-7 years	twice yearly
		6-7 years	twice yearly
	Analysis and synthesis of geometric forms	6-7 years	twice yearly
	Learning strategies (Concrete operations (Piaget))	6-7 years	once yearly
		6-7 years	once yearly
2. Nutrition			
	Food consumption (child)	0-2 years	monthly
		2-3 years	quarterly
		3-4 years	twice yearly
		4-5 years	once yearly
	Family food consumption	3-4 years	twice yearly
		4-5 years	once yearly
	Clinical signs of child's malnutrition	0-5 years	fortnightly
3. Health			
	Prenatal and delivery history	—	once
	Pediatric examination; morbidity history of child and of each member of the household	0-5 years	fortnightly
4. Mother-child interaction			
	Time-sample observation and inventory of home stimulation	0-3 years	monthly
		0-3 years	quarterly
		3-4 years	twice yearly
		4-5 years	once yearly
5. Sociocultural characteristics			
a. Familial			
	Family composition and organization; family type; family size;	0-5 years	once yearly
	main source of income and annual income;	0-5 years	once
	sanitary facilities; social morbidity; social change; informal communication net; mortality record	0-5 years	fortnightly
b. Parental			
i. Biological			
	Age, weight, height	0-5 years	once
	Parity and reproductive history[a]	0-5 years	once yearly
ii. Sociocultural			
	Personal cleanliness	0-3 years	monthly
		3-5 years	thrice yearly
	Formal education and contact with mass media	0-5 years	once yearly
	Nutritional knowledge[a]; health education[a]; proclivity toward change[a]; cultural mobility[a]	0-5 years	once
	Psychologic profile[a], maternal attitudes; intelligence performance[a]	0-5 years	once

[a] Mother only.

Language Development and Malnutrition

Having described in detail the setting of the study and the birth cohort, we would now like to present the preliminary results of the study of certain language features in a group of children who developed severe clinical malnutrition.

During the first five years of life of the cohort, 22 children—14 girls and eight boys—were found to be suffering from severe clinical malnutrition. It must be said that such cases appeared despite all medical efforts to prevent them. The patients' age at the time of diagnosis ranged from four to 53 months, with only one child below one year of age, nine children between one and two years, eight between two and three years, three between three and four years, and one child 53 months of age.

Fifteen of the 22 cases matched the clinical picture of kwashiorkor; the other seven cases were of the marasmic variety (*1*). The proportion of marasmus in females and males was 4:3, but the number of females with kwashior-

kor was twice the number of boys. Because of the small number of cases, these differences are not of statistical significance.

Ten children, six with kwashiorkor and four with marasmus, were treated at home, and nine children with kwashiorkor and three with marasmus were treated in the hospital. The average duration of hospital stay was 30 days, and none of the children stayed longer than 60 days. No deaths occurred in the hospital-treated group. In contrast, three of the 10 children treated at home died. Of the latter, two had kwashiorkor and one had marasmus; their respective ages at the time of diagnosis were 12, 14, and 22 months. All three patients who died did so within 15 to 60 days of diagnosis. Of the 19 survivors, one child emigrated from the village after his discharge from the hospital, leaving a total of 18 cases for study.

In the present report, perceived language development in the 19 children who developed clinical severe malnutrition before the age of 39 months has been compared with the language development of a group of children of the same birth cohort who were never considered as severely malnourished and who were matched at birth for gestational age, body weight, and total body length.

As may be seen in Table 6 and Figure 21, mean language development, as measured by the Gesell method (*14*), is very similar in index patients and controls during the first

Table 6. Language development scores of severely malnourished children and matched controls (days' equivalent).

Age (days)	Birth	180	360	540	720	900	1080
Past or present severe malnutrition	27 ± 3.2	167 ± 14.4	289 ± 47.2	385 ± 86.0	467 ± 102.7	534 ± 103.0	657 ± 119.5
Controls	28 ± 1	177 ± 21.2	334 ± 55.4	490 ± 73.3	633 ± 93.4	785 ± 143.1	947 ± 135.2
"t" test	1.37	1.69	2.69[a]	3.90[a]	4.80[a]	5.80[a]	6.53[a]

[a] Significant at less than 0.01.

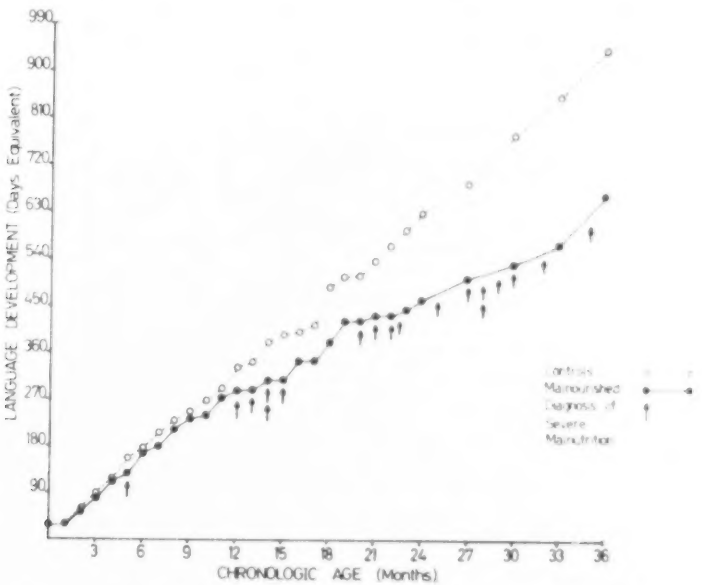

Figure 21. Mean language development as age function in severely malnourished children and matched controls.

year of life when only one case of severe malnutrition had been diagnosed. As time elapsed and more children came down with severe malnutrition, a difference in language performance favorable to the matched controls became evident. The difference was more pronounced at each successive age tested.

Not only were mean values significantly lower in the index cases, the distribution of individual scores was also markedly different from that obtained in the control group. Thus for example, at three years of age (Figure 22), 11 children of the control group had language scores above 1,021 days' equivalent and only one child scored below 720 days. In contrast, while none of the children with past malnutrition scored above 960 days' equivalent, 12 children had values below 720 days and three of these children had language performances six months below those shown by the control children with the lowest scores.

Concept development and particularly the emergence of verbal conceptions have long been viewed as a basic factor in the development of human intelligence. The emergence of the conception of opposites and with it bipolar labelling represents an early and readily measured aspect of the development of concepts in young children. As a consequence of

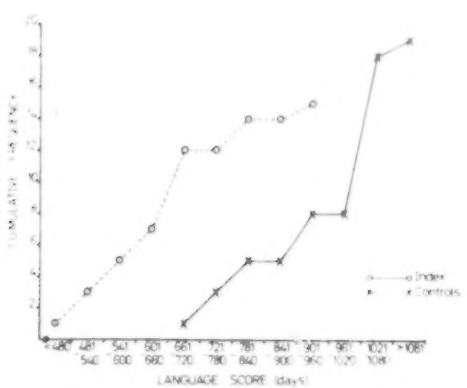

Figure 22. Distribution of language scores at 1,080 days of life of index patients and controls matched at birth for sex and body length.

their concern with improving the school performance of disadvantaged children, Francis H. Palmer and his colleagues at the Institute for Child Development and Experimental Education of the City University of New York, formed the view that the development of a progressively more difficult series of bipolar concepts could be used for the systematic training and enrichment of language experience. Accordingly, as part of their studies on the effects of intervention programs started at age two, they developed a test covering both "poles" of 23 concepts (e.g., big-little, long-short, in-out) in two different situations. Most of the items included require the child to select an object representing a given pole from two objects differing only with respect to their position on one of the concepts' continua. The items are grouped into two forms so that each form contains items covering both poles of each concept. The forms differ only with respect to the setting in which the concepts are placed. The score derived from the test provides a measure of the child's knowledge of various categories that are commonly used in organizing sensory experience.

Although Palmer and his associates have not viewed the series of bipolar concepts that were developed to be a language test, it is implicit in their protocols that the progressively more difficult training series could indeed be used in itself without training as a measure for assessing the natural acquisition of bipolar concepts in young children. To test this hypothesis, we administered 22 of the 23 concepts selected by Palmer as a repeated test of bipolar concept acquisition at ages 26, 31, 34, and 38 months to a total cohort of children living in a preindustrial society (9). All items were presented to the 229 children at all ages independently of the number of successes or failures. In all instances the order of presentation was the same, beginning with the first item contained in Form I. Data obtained at the successive ages tested clearly demonstrated a developmental course of competence in re-

sponse to tasks involving the utilization of bipolar concepts.

The competence in bipolar concept acquisition in children with past or present severe malnutrition and matched controls at successive ages is presented in Table 7, and illustrated in Figure 23. As may be seen, the mean number of bipolar concepts present in the index children is significantly lower than the mean number of concepts shown by the control group. It is important to remember that after 40 months all the children included in the malnourished group actually represent cases rehabilitated from severe clinical malnutrition, i.e., survivors considered as cured of the disease. It may be noted in this respect that the mean value found in the index cases at 46 months of age is almost twice the value obtained at 38 months. Nonetheless, the increment is not enough to bring the index children to the value shown by the controls. In other words, the lag in language development found in severely malnourished children continued to be present after clinical recovery had taken place.

It has been repeatedly stated that human malnutrition does not occur in a vacuum, but that malnutrition is the outcome of an ecologic situation characteristic of the preindustrial societies (*8*). Because we are confronted by a phenomenon with multiple causation, before interpreting our findings as due to the antecedent of severe malnutrition it is necessary to try to sort out what other factors beside the nutritional deficiency may be operating to interfere with the normal development of these children. In trying to answer this question

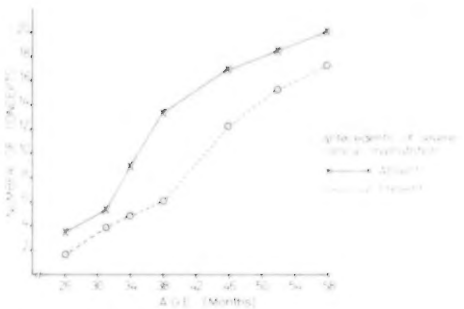

Figure 23. Number of bipolar language concepts present in children with and without antecedents of severe clinical malnutrition.

we have compared the macroenvironment and some features of the microenvironment of the families of the severely malnourished children and of the matched control group.

Broadly considered, the macroenvironmental factors are of three kinds relating, first, to the parents as biologic and social organisms; second, to the family structure; and third, to objective circumstances of life such as sources of family income, income per capita, and sanitary facilities present in the household. Since a detailed description of these factors has already been presented, we will consider now the association of each one with the presence or absence of severe malnutrition.

Biologic characteristics of the parents

The variables in age, height, and weight of either parent, number of pregnancies, and number of live children in the family failed to discriminate between families with and without severely malnourished children.

Table 7. Mean number of bipolar concepts in children with past or present severe malnutrition and in matched controls.

Age (months)	26	31	34	38	46	52	58
Past or present malnutrition	1.61 ± 1.26	3.92 ± 2.56	4.85 ± 3.15	6.07 ± 2.94	12.16 ± 4.13	15.35 ± 3.05	17.21 ± 2.60
Controls	3.54 ± 2.11	5.46 ± 2.96	8.92 ± 3.26	13.42 ± 3.56	16.92 ± 3.26	18.42 ± 3.29	20.07 ± 1.38
"d" test	2.68[a]	1.42	3.36[b]	5.97[b]	3.23[b]	2.57[a]	3.66[b]

[a] Significant at less than 0.05.

[b] Significant at less than 0.01.

Sociocultural characteristics

No significant relationship was found between the presence or absence of severe clinical malnutrition and the variables of personal cleanliness, literacy, and educational level.

Contact with information mass media was explored through literate parents' newspaper reading and radio listening. The number of mothers or fathers of malnourished children who were regular newspaper readers was not different from the number who were in the matched control group. Similarly, the number of fathers who listened regularly to the radio was the same in both malnourished and control groups. As may be seen in Table 8, the case of the mothers was different. There were almost equal numbers of radio listeners and nonlisteners in the malnourished group, but the number of listeners among the matched control group was more than three times the number of nonlisteners. The difference is significant at the 0.05 level of statistical confidence (Chi square = 4.20; Df = 1; $p < 0.05$).

Family structure

The variables of family size and type of family (nuclear or extended) were not found to differentiate between the malnourished and control groups.

Family economic status

The socioeconomic status of the families was estimated using four indicators: main source of family income, sanitary facilities in the household, annual income per capita, and percentage of total expenditures spent on food.

Table 8. Radio listening by mothers of severely malnourished children and matched controls.

Mothers of	Radio Listening		
	Yes	No	Total
Severely malnourished children	8	10	18
Matched controls	14	4	18
Total	22	14	36

$X^2 = 4.20$; Df = 1; $p < 0.05$.

No significant associations were found between any of these four indicators and the presence or absence of severe malnutrition.

In summary, of all the features of the macroenvironment considered, the only differential between severely malnourished children and controls, matched at birth for gestational age, body weight, and total body length, was the mother's contact with the world outside the village through regular radio listening. None of the other characteristics of the parents (biologic, social, or cultural) or familial circumstances, including income per capita, main source of income, and family size, were significantly associated with the presence or absence of severely malnourished children.

Since the features of the macroenvironment could not explain severe malnutrition, our attention has turned toward the analysis of the microenvironment of the two sets of children. We have selected the potential stimulation of the home as our first general indicator of the quality of child care, and of the mother as the principal stimulating agent for young children.

The instrument used for estimating home stimulation was the inventory developed by Beattye Caldwell (3). This inventory was designed to sample certain aspects of the quantity and, in some ways, the quality of social, emotional, and cognitive stimulation available to a young child within his home. Two forms of the inventory were used, one designed for infants up to three years of age, and the other for children three to six years old. In both versions the selection of items included has been guided by a set of assumptions about conditions that foster development. Accordingly, the inventory describes and quantitates eight areas of the home environment: (1) frequency and stability of adult contact; (2) vocal stimulation; (3) need gratification; (4) emotional climate; (5) avoidance of restriction; (6) breadth of experience; (7) aspects of the physical environment, and (8) available play materials. In each of these areas almost all

items receive binary scores and no attempt is made to rate finer gradations. The total score is the number of items recorded as positive for the child's development. If it is desirable, each area may be scored separately and related to specific features of development.

A trained psychologist recorded the inventory of home stimulation in every child in the cohort at six-month intervals during the first three years of life and at yearly intervals thereafter. At the time of data collection and scoring, the psychologist was unaware of the nutritional antecedents of the children.

Figures 24 and 25 show the distribution of home stimulation total scores obtained in malnourished and control children at six and 48 months of age. As may be noted, even at six months, when only one case of severe clinical malnutrition was present, the control children had significantly higher home stimulation scores. Thus, while none of these children had homes with less than 30 points, almost one-fourth of the homes of the future malnourished children scored below 30 and almost one-half had scores below 32 points. Similarly, at 48

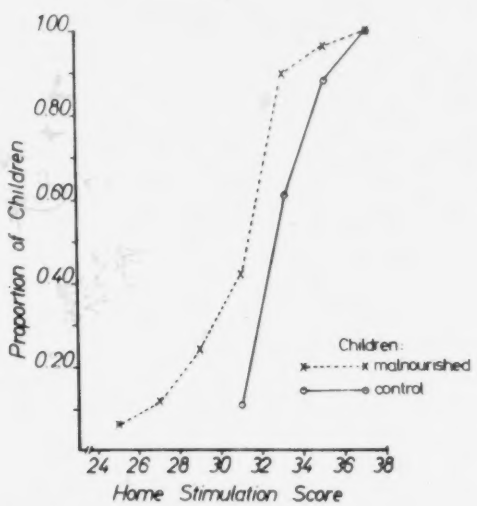

Figure 24. Proportion of malnourished and control children showing different home stimulation scores at six months of age.

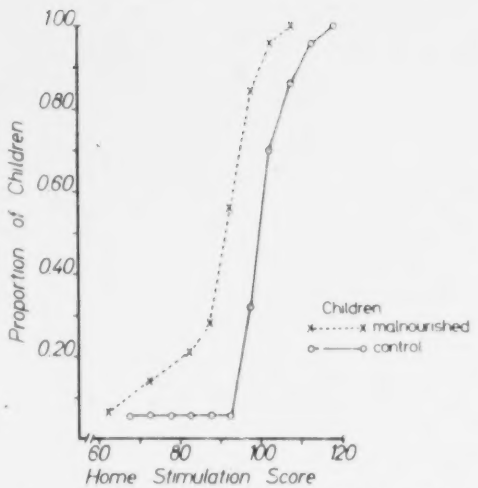

Figure 25. Proportion of malnourished and control children showing different home stimulation scores at 48 months of age.

months of age children who had recovered from malnutrition were living in homes whose scores in home stimulation were well below those in which the control children were living. In a range of scores from 60 to 120, about one-half the survivors from severe clinical malnutrition had home stimulation scores below 94 points and only one home had a score between 105 and 109. This distribution of scores is markedly different from that shown by the homes of the control children, among which only one had a score below 95 while four reached values between 110 and 120. These differences are statistically significant at the 0.01 level of confidence.

The difference found in the quality of home environment between severely malnourished children and matched controls points toward the value of analyzing other features of the microenvironment. The association between the presence of severe clinical malnutrition and the mother's psychologic profile, maternal attitudes, proclivity toward change, concepts of health and disease, concepts of food and feeding, and family visiting pattern is now under analysis.

Since on the one hand the presence of severe malnutrition was significantly associated with home stimulation, and on the other survivors of severe malnutrition showed a significant lag in language bipolar concept formation, it seemed logical to investigate the interrelations among these three factors in order to estimate their possible role. As a first approach to this issue a technique of partial correlation was used to look at the degree of association between two variables "holding constant" the influence of the third variable. Since the number of cases of malnutrition was rather small, we decided to test for interrelations in the total birth cohort.

The coefficients of correlation product × moment among home stimulation scores, total body height, and number of bipolar concepts present at 46 months of age in the total cohort (229 children) were:

Home stimulation score:
Number of bipolar concepts = 0.20
Home stimulation score:
Total body height = 0.23
Total body height:
Number of bipolar concepts = 0.26

When the relation between home stimulation and number of bipolar concepts was partialed out for body height, the coefficient of correlation dropped from 0.20 to 0.15. When the relation between body height and number of bipolar concepts was partialed out for home stimulation, the coefficient changed from 0.26 to 0.23. Finally, when the number of bipolar concepts was "held constant," the coefficient of correlation between home stimulation and body height changed from 0.23 to 0.19. These results suggest that the association between home stimulation and number of bipolar concepts is mediated to a good extent through body height, which in turn holds a significant degree of association with the number of bipolar concepts independently—to a large extent—of home stimulation. Within the limits of the probabilities given by the magnitude of the coefficients, home stimulation contributes relatively more to body height than to number of bipolar concepts, while body height contributes more than home stimulation to the variance of bipolar concepts. Other forms of statistical approach to the problem of the relative contribution of several variables to both the presence of malnutrition and the presence of somatic and mental lags in survivors, such as regression analyses and multivariate analysis of variance, should be tried to obtain a more quantitative answer to this subject.

With the results now available, one can fairly state that (1) susceptible infants cannot be identified before the development of severe clinical malnutrition since they do not differ from the rest of their birth cohort somatically or behaviorally; (2) the appearance of severe clinical malnutrition seems to be associated, in preindustrial communities, with features of the microenvironment; (3) children who have recovered from severe clinical malnutrition lag behind controls in language development, but poor microenvironmental conditions are not sufficient to fully explain the behavioral lag, and (4) how long the survivors will perform below the matched controls' values still lacks an adequate answer.

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SUMMARY OF SESSION II

Jack Tizard[1]

The five papers in our second session had certain common elements. Dr. Klein and his colleagues in Guatemala have been studying children born in four Guatemalan villages during the last five years, and he has presented some of his preliminary findings on psychologic test performance and its implications. The object was to elucidate the relations among various measures used to assess the effects of dietary supplementation upon growth and development. Like the other speakers today, Dr. Klein was concerned with the development of measures as well as the development of children. Among the measures he has used are indicators of socioeconomic status and psychologic functioning, as well as indicators of nutrition and of the child's physical growth. The message reported was a twofold one: first, we cannot say that "performance" is determined by one set of factors rather than another, and second, for predictive purposes we need to adopt more complex models than the simple additive or correlative ones that are commonly used.

Dr. Klein's paper raised a number of questions. One is the definition of an adequate psychologic test—something that came up in one way or another in all the papers—and which indeed constantly arises in work with children who differ from the samples of North American, British, or other European populations that have been used to standardize most of our tests. To simplify the presentation of his findings, Dr. Klein picked out a number of particular subtests—four psychologic subtests out of 40—which he used as the basis for his arguments. I think that this was probably a mistake. With mental test data one finds that the validity of individual items and subscales is almost universally low, even when the validity of scales made up of numbers of items is very high. Thus, correlations between scores on individual items in a Binet test, for example, may be as low as 0.3, but when you add a number of these carefully selected items together you get highly reliable test scores that also have a substantial face validity. I should think that when one has given a number of ad hoc tests of a general kind, the first and most successful next step would be to examine the way in which scores on different subtests are related one to another. One might be able to add items or subscales, and so derive indicators that were of high reliability and evident face validity. Once one had such indicators, the way would be open for more sophisticated analyses of the significance of differences in scores obtained on the various factors believed to exert an influence on performance.

Perhaps the most interesting aspects of Dr. Klein's presentation came out during the following discussion rather than in the paper itself. He told us that the growth rates of children whose diets had been adequately supplemented were not significantly different from those of well-fed North American children, but they were vastly different from those of children in control villages and in the rest of Guatemala. We would all have liked to examine these data in detail.

Dr. Klein also told us in the discussion about observational studies which he has been carrying out. Data collection on the rate and frequency of social and physical contact between mother and child is laborious, and the data are difficult to score, he reports. I do hope, however, that he will not too readily give up the further collection and analysis of this kind of

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material. Inasmuch as it bears on the quality of life of children, it is likely to be most important to an understanding of the outcome of severe malnutrition, just as it is likely to contribute greatly to our knowledge of the concomitants and effects of chronic subnutrition.

The Mexican studies reported on by Dr. Cravioto in his masterly paper represent the work of a large team of careful investigators who in 15 years or so have developed indicators they are now able to use very effectively to answer specific questions. The careful description of a particular village—the "Village of the White Dust," which must by now be the most famous village in Mexico—is, I think, a necessary beginning to longitudinal study of the sort in which Dr. Cravioto is engaged.

Dr. Cravioto arrested our attention by telling us that despite the presence in the village of three research pediatricians, four psychologists, 10 social workers, two administrators, and several others on the research team, there were still 22 cases of malnutrition there over a period of time. By asking why this should occur, he began to raise issues of the most profound clinical as well as social importance. He analyzed in detail the macroenvironment of the families of these children and of a matched control group, and showed them to be similar. Then he went on to analyze the microenvironment of the two sets of families to show why some children living in very poor circumstances developed clinical malnutrition, whereas others did not. The answer seemed to be very clearly related to differences in the qualities of the microenvironment. It follows that if one is going to intervene to cut down the incidence of severe malnutrition, one has to find ways to influence the microenvironment. A careful description of the qualities of this environment is an essential first step toward this goal.

Dr. Mönckeberg's paper again reminded us of the recurring cycle of malnutrition, poverty, and poor health and environmental circumstances, and of their blighting effects on the development of children. He pointed out that Santiago children who are not dropouts or early leavers but remain at school are those who are taller, heavier, and better fed and who have higher IQs and better school performance. In a tantalizingly brief account, he reported on a study in Colombia in which a systematic attempt is being made to vary physical and cognitive stimulation and to supplement the feeding of children of different ages in order to examine differences in outcome. It was impossible from his brief description to get a clear picture of this study, however. It is fairly elaborate and very ambitious, but if it can be carried through it seems likely to yield results of profound importance for our understanding of recovery from malnutrition.

I would like to take issue with one of the conclusions Dr. Mönckeberg drew from his Chilean studies of the effects of intervention with a group of children aged seven to nine years. A nine-month dietary supplement resulted in an increase in the height and weight of the children, but no increase in intelligence. From this Dr. Mönckeberg appears to have concluded that by the age of seven it was all a bit too late, that no intervention after the age of five or six was likely to be very effective in shifting IQ. It is not legitimate to assume this from one particular study, in which in any case no special attempt was made to provide mental stimulation. Furthermore, there are other studies which show that changes in life circumstances can bring about substantial increases in intellectual functioning even if they occur during late adolescence. Husén, for example, in a study of young men entering the Swedish Army, compared the IQs they achieved at call-up with their IQs at 11 years of age. Those who had left school early had markedly lower IQs at the age of 18 than those of identical 11-year-old IQ who had continued longer in school. Similarly, Alan Clarke has shown that mildly retarded young men and women who in adolescence enter a mental subnormality hospital (in itself a pretty unstimulating environment, but one perhaps more stimulating

than the environments in which they were living before admission) are likely to increase in intelligence.

The point is, we simply cannot afford to give up in adolescence, nor indeed does the evidence suggest that mental performance is immutable by then. What we must do is to learn from what I understand the Cubans and the Chinese are doing, namely to think about the wholesale education of adults as well as children. It is perfectly true, as Dr. Mönckeberg has said, that if we are to solve the problems of malnutrition on a world scale, something like a new environment will have to be created, but to say this is not in itself very helpful. We have also to look at all stages and ages to see what possibilities are open to us in an imperfect world.

The studies in Uganda and Jamaica were similar in many respects: they both investigated the long-term effects of malnutrition in infants and young children admitted to research wards in a university hospital. They also inquired into the age of acute illness and its relationship to outcome. Interestingly, though these two studies were both carried out at about the same time and by people working in British Medical Research Council units, none of those who took part in either study was more than barely aware that the other study was being carried out. This raises the question of how communication can be improved. I do not think the answer is through newsletters in which people are asked to write about projects they are just about to undertake.

Despite a lack of communication between those taking part in the Kampala and Jamaican studies, the two investigations had much in common, both in methodology and the conclusions that stemmed from them. The Jamaican study showed in a population at risk that children hospitalized because of an acute episode of severe malnutrition are likely in later childhood to be shorter, less intelligent, poorer in school performance, and less socially competent and to weigh less than their classmates. Differences between the severely malnourished children and their sibs are less clear. Furthermore, the study produced no evidence to suggest that children admitted to hospital after the first nine months of life were less likely to be physically or mentally stunted in later childhood than those admitted before nine months. It did suggest, however, that when the post-hospital environment was more intellectually stimulating, the outcome was likely to be better than among children growing up with poorer intellectual stimulation. This is the only cheerful feature in a set of otherwise melancholy conclusions which are of great social importance.

In the Kampala study it was found that previously malnourished children were stunted relative to their comparisons. Using a wide battery of psychologic tests, the investigators were able to show that certain functions in the malnourished children were significantly depressed whereas other capacities were relatively spared. They also report that motor coordinative activity and intellectual level were significantly lowered in the previously malnourished children. The studies' main difference lies in the Jamaican attempt to explore the background histories of the children to determine what social and biologic factors besides nutrition influence the children's current level of functioning.

All the work we have described clearly points up the need to develop better attainment and outcome measures for children of different cultures. Measures of the performance of individual children are perhaps better developed than measures of home stimulation. Caldwell's Index is probably the first not wholly unsatisfactory measure that we have of home stimulation, but it seems evident that we have a long way to go before we can really assess the quality of the child's microenvironment in a satisfactory way. Both Dr. Cravioto's and Dr. Richardson's papers give us some idea of the ways in which we can approach this task.

Even with the measures we already have, comparisons can be made between subgroups living in particular cultures. It is much more difficult, and indeed it may be impossible in the short term at any rate, to carry one's comparisons across cultures. But if the same kind of functional relationships are found to obtain first in one culture and then in another, we do gain confidence in their generality. Thus, though different operational measures of intellectual stimulation were employed in the Jamaican and Mexican studies, both revealed that the severely malnourished children had experienced less intellectual stimulation than their comparisons.

It should also be noted that the studies today are showing the need to ask more, and more sophisticated questions. We are already looking much more analytically than in the past at the nature of psychologic deficit and at the interactions among sociocultural and nutritional variables that are responsible for poor performance, for example. I hope that we will soon be hearing reports of other studies in which the efficacy of different types of treatment regimen is compared. The stage will then be set for us to move, in different fields, from epidemiologic and clinical studies which are largely descriptive, to studies that enable us to bring clinical and socially relevant factors under some kind of experimental control.

My final point concerns the relevance of animal data to human epidemiologic and clinical study. Dr. Stewart's research and some of the other work mentioned yesterday indicates that future studies are likely to be much more than biochemical. Theoretical and methodologic problems exist that are greatly elucidated by animal experiments and models, and comparative psychologists have in recent years been pursuing them with great sophistication and conspicuous success.

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Session III

ECOLOGY OF MALNUTRITION

Chairman

Fernando Mönckeberg

Rapporteur

Joaquín Cravioto

ECOLOGY OF MALNUTRITION: NONNUTRITIONAL FACTORS INFLUENCING INTELLECTUAL AND BEHAVIORAL DEVELOPMENT

Stephen A. Richardson[1]

Introduction and Review

In the report of the International Conference on Malnutrition, Learning, and Behavior held in 1967 at the Massachusetts Institute of Technology, the editors made the following comment on the ecology of malnutrition:

> With the wide variety of determinants already identified, the approach becomes clear; it is ecological—the interplay between man as a biological organism and as a human being, and the whole of the many-sided environment in which he lives (*22*).

In his introduction to the session, the moderator, Dr. William Darby, stated:

> Of necessity, the test of early malnutrition as a determinant of learning and behavior in man is through field study of people in their natural setting, exposed to all the influences that determine intellectual capacity and behavior patterns. . . . The aim of the field study is to sort out the relative contribution of malnutrition among a variety of other factors (*22*).

The purpose of many studies presented at that conference was to investigate the long-term consequences of malnutrition during pregnancy and the early life of the offspring. In almost all the studies a quasi-experimental design was used in which the attempt was made to hold constant all ecologic variables except nutrition that might impair functional development. One design was an experimental intervention model using two human populations that were as nearly as possible equivalent in all respects and in which severe malnutrition was prevalent during pregnancy and early childhood. Food supplementation was given one of the populations without any other change. The later intellectual and behavioral functioning of the children in the two populations was subsequently measured. A study using this approach was outlined by Canosa (*4*).

To meet the requirements of this design, it is necessary to determine that severe malnutrition does occur in pregnant women and infants in the two populations; that supplementary feeding occurs in the experimental group, and that the food given is used as a supplement and not as a substitute; that the supplementary feeding does not change other factors (or that these other factors are changed in the control group) and that all factors that influence intellectual and behavioral development in the children studied are the same in the experimental and control populations. A satisfactory study must identify and measure the factors other than nutrition that affect the functional development of children and not merely assume their equivalence in the experimental and control groups. Such a study must begin before the

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mother's pregnancy and continue during the infancy of the offspring and into school age until the behavioral and intellectual level of children can be tested with measures that have predictive value. To meet these experimental requirements, a number of very difficult practical and ethical problems must be overcome.

A second quasi-experimental approach depends on "natural" intervention (*3*, *5*, *6*, *23*). In this type of approach a group of children who were known to have been severely malnourished in infancy are identified, and an attempt is made to find a matched control child for each malnourished child. The controls must not have been severely malnourished, and ideally must be matched for all biologic and social factors that contribute to later intellectual and behavioral functioning. In practice the cases called "controls" have been matched with the experimental cases on such variables as age, sex, socioeconomic status, and being in the same classroom at school. An alternative has been to use the malnourished child's sib as a comparison (*1*, *14*). Here the assumption is made that by living in the same family the index child and sib will have experienced very similar ecologic conditions. They will necessarily differ in age, pregnancy number, and ordinal position within the sibship, and they may differ by sex unless this is used as a control variable. In these studies the assumption is made that all factors other than the control variables are held approximately constant, or that what variation does exist is randomly distributed between cases.

The quasi-experimental approaches have inherent limitations. One is that if all variables except nutrition that influence the functional development of the child are controlled, it would prevent the study of variations in all variables except malnutrition. It limits the study of interaction effects between nutrition and the other ecologic factors, or the varying circumstances and conditions under which malnutrition has differential effects on later functioning. It is reasonable to expect that the consequences of severe malnutrition vary widely depending on the ways in which other biologic and social factors influence a particular child. The interaction of background factors related to the intelligence of children may be illustrated from the following report of a study of school children in Scotland:

> The purpose was to examine the association between combinations of birth weight and gestational age, and later intellectual functioning of the children. Further, we wished to see whether low birth weight and gestational age would have different associations with the child's intelligence at age 7 depending upon the general life styles in which the child lived. We therefore looked at the associations for each social-class category separately. In order to avoid the effects of obstetrical and neonatal complications, any cases with such complications were removed and analyzed separately . . . [The analysis was also restricted to children who had not been administratively classified as mentally subnormal. We had found separately that low birth weight] . . . and low gestational age were more frequent for mentally subnormal children than for children who were not mentally subnormal.

Figure 1 shows the average IQ of children with different birth weights and gestational ages within each social class category. For each social class, children with birth weights of less than 5 pounds and gestational age of less than 37 weeks have lower IQ scores than the average IQ for all children within the same social classes [Table 1]. With the exception of the upper social class I-IIIa, when children have experienced both low birth weight and low gestational age, they have lower average intelligence scores than when low gestational age was present, but not low birth weight. The size of difference in average IQ between all children in a social class and the children with low birth weight and gestational age is larger in the lower than in the upper social classes. This suggests that there is a biosocial interaction, with children of lower social class families at greater risk of intellectual impairment from low birth weight and

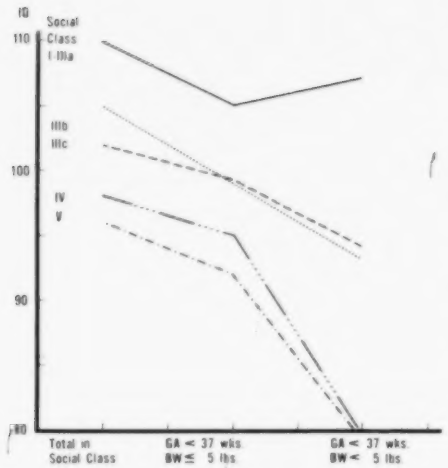

Figure 1. IQ test scores and social class of seven-year-old children with different gestational age (GA) and birth weight (BW) in Aberdeen, Scotland, 1962. Cases with evidence of obstetric complications or low physical grade at birth were excluded.

gestational age than children from upper class families (*20*).

This study shows the way in which low birth weight and shorter gestation appear to have more severe affects on intelligence in children who live in a lower-social-class family.

Table 1. IQ test scores and social class of seven-year-old children with different gestational age (GA) and birth weight (BW) in Aberdeen, Scotland, 1962.

Social class	Number	Average IQ
I-IIIa		
Total in social class	1,556	110
GA < 37 wks., BW ≥ 5 lbs.	37	105
GA < 37 wks., BW < 5 lbs.	9	107
IIIb		
Total in social class	1,490	105
GA < 37 wks., BW ≥ 5 lbs.	18	99
GA < 37 wks., BW < 5 lbs.	13	93
IIIc		
Total in social class	1,310	102
GA < 37 wks., BW ≥ 5 lbs.	29	99
GA < 37 wks., BW < 5 lbs.	16	94
IV		
Total in social class	939	98
GA < 37 wks., BW ≥ 5 lbs.	22	95
GA < 37 wks., BW < 5 lbs.	7	<80
V		
Total in social class	864	96
GA < 37 wks., BW ≥ 5 lbs.	42	92
GA < 37 wks., BW < 5 lbs.	10	<80

A second limitation of quasi-experimental designs in the study of severe malnutrition is the highly questionable assumption that through controlling variables such as socioeconomic status, however defined, all factors that influence the intellectual and behavioral functioning of children are also controlled. This is recognized in the discussion of most of the studies.

The literature on malnutrition in childhood suggests some of the ecologic factors that need to be considered. Cravioto and his coworkers (*7*) give a schematic presentation of the interrelation among biosocial factors and low weight gain. Richardson (*17*) discusses the influence of social, environmental, and nutritional factors on mental ability, and Kallen (*11*) provides a schema of interdependent, interacting factors determining learning. Hansen and coworkers (*9*) suggest that retardation of growth and development occurs with ". . . poverty, inadequate maternal care, disturbed family relationships, overworking, lack of educational and play facilities, illness, scant medical facilities and general paucity of the cultural environment." These presentations are suggestive and descriptive. There is need for fuller and more systematic consideration of factors other than nutrition that influence the functional development of children, however. There is also need to develop malnutrition research that incorporates these ecologic factors into the research design, data gathering, and analysis. The remainder of this paper is a consideration of these two issues.

Identification of Ecologic Factors Influencing Functional Development

Even a cursory review of the social and biologic research literature dealing with factors that influence the intellectual and social development of children reveals a diverse and formidable array of theory, concepts, research reports, inferences, and speculations. Certainly

no investigation can deal systematically with all the known and suspected factors that influence the functional development of children, but the study of selected background factors judged to be salient is possible and provides an essential basis for examining the relative importance of the influence of malnutrition compared to other ecologic factors.

The ecologic factors shown in Figure 2 are illustrative of what may be derived from a review of the general topics of social and human deprivation, child development, pediatrics, and obstetrics (*8, 12, 13, 15, 16, 21, 24, 25*). In developing the list of factors, the background of the malnourished children was considered in terms of factors that influence the functional development of children and may be biologic, social, physical, or technologic in nature. One useful way of looking at a wide variety of background factors is to consider the material and human resources that are brought to bear in the care and upbringing of the child. Some ecologic factors may have a pervasive effect that influences many of a child's functional modalities. Other factors may have more limited influence and affect a single function of the child.

The outcome measures of functioning of children should include not only anthropometry and IQ, which have been the major preoccupation of investigators studying the long-term effects of malnutrition, but also measures of school performance, cognitive functioning, behavior, level of health, and indicators of central nervous system impairment.

The list of factors presented in Figure 2 was developed for a study in Jamaica of the long-term consequences of severe malnutrition in the first two years of life. Because data from that study will be used to illustrate points in this paper, a brief description of its research design is necessary.

Boys who had been hospitalized with the primary diagnosis of severe malnutrition sometime during their first two years of life were selected for study. They were traced when they were between six and 10 years of age. For each malnourished boy (n = 74 index cases), two boys were also chosen for study who had not been severely malnourished: the sib of the index case of the same sex and nearest in age (n = 38 sibs) and a classmate of the index case of the same sex and nearest in age to the index case (n = 71 comparisons).

Figure 2. Ecologic factors.

- **Child's Biologic Mother**
  - Reproductive history
  - Health history
- **Mother's or Caretaker's Capabilities and Activities**
  - Verbal ability
  - Values
  - Exposure to ideas
  - Activities and affiliations
  - Human resources
  - Training and upbringing of the child
  - Aspirations for the child
  - Mother as teacher of the child
- **Father or Adult Male**
  - Presence of adult male role model in the household
  - Existence of affectionate ongoing relationship with the child
  - Joint activities of husband and wife with the child
  - Degree of conflict or cooperation between husband and wife in childrearing
- **Family**
  - Composition
  - Stability
  - Extended family
  - Social relations between family, friends, and neighbors
  - Alternative caretakers available for the child
- **Physical and Economic Resources of the Family**
  - Income in cash and kind
  - Type and size of dwelling
  - Water supply
  - Availability of electricity
  - Appliances
  - Type of fuel used
  - Transportation
- **Area of Residence**
  - Spectrum ranging from isolated rural location to large urban center
- **Child's Background History**
  - Pregnancy number and ordinal position
  - Birth weight and general health history (other than malnutrition)
  - Feeding during the first two years of life
  - Continuity in prime caretaker
  - Continuity in composition of family
  - Relationships with adults
  - Relationships with other children
  - Exposure to ideas and language
  - Activities and experiences outside the home
  - School history

For each boy in the study a detailed psychologic, anthropometric, and pediatric neurologic assessment was made. Their schools were visited to obtain their teachers' assessments of the boys' school performance and behavior. Home visits were made to obtain comprehensive information on the child's social and biologic history and a range of ecologic factors that may have influenced his functional development. The factors in Figure 2 vary widely in levels of abstraction, and the translation of these factors into data collection procedures is a major undertaking. The procedure must be partly inductive because the specific questions, observations, or use of documentary sources must be meaningful and relevant to the particular society and culture in which the study is undertaken. The procedure must also be partly founded on previous research or theory to provide a basis for selection among the almost infinite number of variables that might be identified.

Translation of Concepts into a Data-Gathering Procedure

There is a conceptual procedure that must be undertaken regardless of where a study is conducted. This involves the translation of each of the general factors that may influence the child's functional development into the specific units of information to be obtained in data collection. The procedure can best be explained by means of an illustration from the Jamaican study. Conceptually, an important factor in the development of a child is "intellectual stimulation." This is an abstraction that needs to be reduced to the various specific ways in which a child receives intellectual stimulation: for example, being read to aloud or being told stories, having pictures to look at and materials for drawing and painting, contact with mother or principle caretaker having a good command of language, conversing with and encouraging the child to talk and think about things. Observations or questions that will get information on these indicator variables have to be developed in careful pretesting. Seven questions used in Jamaica as indicators of intellectual stimulation will serve as an illustration. The questions were:

1. Does he have any toys you or anyone else has given him?
2. Does he have any books or magazines?
3. Does he listen to the radio?
4. Does [child's name] watch TV?
5. Have you or anyone else taken [child's name] on trips to other places besides the visits to relatives and friends you have told me about?
6. Does anyone tell him stories?
7. Does anyone read to him?

Questions were asked of the child's mother or principle caretaker and answers were coded as "yes," or "no," or "do not know."

Data Analysis

In undertaking the analysis of functional outcomes, we already knew that the malnourished children were significantly smaller, had lower IQ's and school performance, and were more impaired in behavior in the school setting (*2, 10, 18, 19*).

Each question in the intellectual stimulation index was based on the theoretical prediction that those children for whom negative responses were obtained would receive less stimulation, and that those with less stimulation would have lower IQ, poorer school performance, and impaired social behavior. To test these assumptions, the associations between the answers to each of the questions and measures of the child's functioning were examined separately for the index and comparison children. The strongest evidence in support of the predictions would be a positive association between negative responses to the questions on intellectual stimulation and the presence of impaired or poorer functioning for both index and comparison sets of children. If a positive association is found for the comparison but not the index children, the result might suggest that

malnutrition is sufficiently powerful in its influence to mask the effect of intellectual stimulation. On the other hand, if an association is found for the index children but not for the comparison, the finding might suggest that intellectual stimulation is more influential for malnourished children. If no association is found for either set of children, it suggests these particular indicators of intellectual stimulation are unrelated to functional competence or are not appropriate indicators of intellectual stimulation.

Table 2 shows the associations between the seven indicators of intellectual stimulation and full-scale IQ for the index and comparison sets of children.[1] For the index children all the

[1] Consideration of other functional modalities such as school performance and behavior have been omitted to simplify the illustration. Consideration of the sib is omitted for the same reason.

Table 2. Relationship between indicators of intellectual stimulation and full-scale IQ for malnourished and nonmalnourished sets of boys.

Full-scale IQ	Malnourished (index)				Nonmalnourished (comparison)			
	Toys given child				Toys given child			
	Yes	No	X^2	p[a]	Yes	No	X^2	p[a]
Below median	22	16	0.891	N.S.	23	13	5.937	<0.01
Above median	24	11			31	4		
	Has books or magazines				Has books or magazines			
	Yes	No	X^2	p	Yes	No	X^2	p
Below median	7	31	6.998	<0.005	13	23	3.156	<0.05
Above median	17	19			20	15		
	Listens to radio				Listens to radio			
	Yes	No	X^2	p	Yes	No	X^2	p
Below median	28	10	1.016	N.S.	30	6	0.430	N.S.
Above median	30	6			27	8		
	Watches TV				Watches TV			
	Yes	No	X^2	p	Yes	No	X^2	p
Below median	12	24	6.727	<0.005	14	22	9.040	<0.005
Above median	23	13			26	9		
	Taken on trips				Taken on trips			
	Yes	No	X^2	p	Yes	No	X^2	p
Below median	11	27	6.504	<0.01	12	24	7.445	<0.005
Above median	21	15			23	12		
	Told stories				Told stories			
	Yes	No	X^2	p	Yes	No	X^2	p
Below median	19	19	4.912	<0.025	24	12	0.113	N.S.
Above median	27	9			22	13		
	Stories read to child				Stories read to child			
	Yes	No	X^2	p	Yes	No	X^2	p
Below median	26	12	1.426	N.S.	27	9	0.2541	N.S.
Above median	29	7			28	7		

[a] All probability levels are one-tail due to the directional nature of the hypothesis.

associations are in the predicted direction and four are statistically significant.[2] For the comparison children, four are in the expected direction and all four are statistically significant.

Having examined the indicators of intellectual stimulation separately, they may now be combined into an overall index. This provides some indication of the cumulative effect of responses to the seven separate indicators. Each response is given equal weight because there is no obvious conceptual basis for differential weighting. The overall score ranges from 0–7, a score of 7 indicating maximal stimulation, and a score of 0 minimal stimulation. Table 3 shows a significant positive association between intellectual stimulation and IQ for index and comparison sets ($p < 0.005$ and $p < 0.025$, respectively). This result does not establish that a higher level of intellectual stimulation in childhood causes better intellectual functioning. It only shows an association, and cause can be attributed only through "guilt by association." Nevertheless, the analysis does provide useful evidence.

Having found evidence in support of the hypothesis that children who receive less intellectual stimulation will have lower IQs, it is now worth testing the prediction that the malnourished boys have received less intellectual stimulation than the comparisons who were not malnourished. No significant differences were found between the index and comparison sets of children for any of the seven indicators of intellectual stimulation, although all show a trend in the expected direction. For the overall index of intellectual stimulation (Table 4), however, the association is in the predicted direction at the $p < 0.025$ level of significance.

So far the associations between malnutrition and the children's IQs, and between intellectual stimulation and IQ have been considered separately. To examine the combinations of nutrition and intellectual stimulation, the following four subsets of children were chosen.

1. Malnourished boys low on intellectual stimulation.

[2] All probability levels included in the test and tables are one-tail due to the directional nature of the hypothesis.

Table 3. Relationship between index of intellectual stimulation and full-scale IQ for malnourished and nonmalnourished sets of boys.

Full-scale IQ	Malnourished (index)				Nonmalnourished (comparison)			
	Index of intellectual stimulation				Index of intellectual stimulation			
	Below median	Above median	X^2	p[a]	Below median	Above median	X^2	p[a]
Below median	27	11	9.242	<0.005	22	13	4.629	<0.02
Above median	12	22			13	22		

[a] All probability levels are one-tail due to the directional nature of the hypothesis.

Table 4. Differences between malnourished and nonmalnourished sets of boys on index of intellectual stimulation.

Index of intellectual stimulation (number of "yes" responses to indicator questions)	Malnourished (index)	Nonmalnourished (comparison)	X^2	p[a]
0-3	28	24		
4-5	30	20	6.974	<0.025
6-7	14	28		

[a] The probability level is one-tail due to the directional nature of the hypothesis.

2. Malnourished boys high on intellectual stimulation.
3. Nonmalnourished boys low on intellectual stimulation.
4. Nonmalnourished boys high on intellectual stimulation.

Based on the previous analyses we would expect subset 1 to have the lowest level IQ and subset 4 to have the highest level. Of particular interest will be the distribution of IQ within subsets 2 and 3 as an indication of the relative salience of malnutrition and intellectual stimulation for IQ. The results of this analysis (Table 5) for the two extreme subsets are as expected. The average IQ for the comparison boys with high intellectual stimulation is 18 points higher than the index boys with low intellectual stimulation. No significant difference is found between the two intermediate subsets (Table 6), and there is an average IQ difference of only two points. Considering the interaction between nutrition and intellectual stimulation, these results suggest that malnourished children with high intellectual stimulation function as well at school age, as measured by IQ as children who have not been malnourished but have received low intellectual stimulation.

To determine whether these results have been obtained largely because of the contribution of a few extreme cases, cumulative percentage distributions for the four subsets of children were prepared (Figure 3). The results show that this is not the case.

The steps outlined for examining the variable of intellectual stimulation may be applied to each of the ecologic factors—both social and biologic—included in a study. A further step would be consideration of various combinations of ecologic factors using different forms of multivariate analysis. As the first step for each child, a profile could be prepared of each ecologic factor and whether it is more or less likely to contribute a positive influence on the

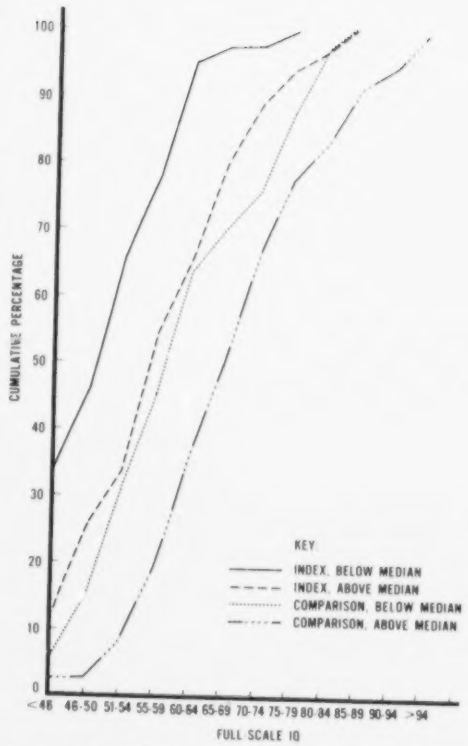

Figure 3. Cumulative percentage distribution of full-scale IQ for malnourished (index) and nonmalnourished (comparison) sets of boys grouped by above and below median of index of intellectual stimulation.

Table 5. Mean full-scale IQs and standard deviation grouped by index of intellectual stimulation for malnourished and nonmalnourished sets of boys.

Subgroup	Number (n)	Mean (X)	Standard Deviation (s)
Malnourished children (index)			
Below median of index of intellectual stimulation	41	52.9	7.7
Above median of index of intellectual stimulation	33	62.7	11.6
Nonmalnourished children (comparison)			
Below median of index of intellectual stimulation	35	60.5	11.1
Above median of index of intellectual stimulation	36	71.4	13.9

Table 6. "t" test results of differences of full-scale IQ means for malnourished and nonmalnourished sets of boys divided by above and below median of index of intellectual stimulation.

Subsets of children	"t"	Probability level
Index[a], below median vs. index, above median	4.17	$p < 0.001$
Index, below median vs. comparison[b], below median	3.41	$p < 0.005$
Index, below median vs. comparison, above median	7.09	$p < 0.001$
Index, above median vs. comparison, below median	0.80	n.s.
Index, above median vs. comparison, above median	2.83	$p < 0.01$
Comparison, below median vs. comparison, above median	3.66	$p < 0.001$

[a] Index (malnourished).
[b] Comparison (nonmalnourished).

child's functional development. The cumulation of these factors provides an overall measure of the identified elements of the ecologic situation that has influenced functional development. The simplest measure of the overall array of ecologic factors would be an above-and-below median split with a score of 1 representing the more favorable end of the index and 0 the less favorable. A high score across the factors would thus represent a favorable ecologic environment. At this stage of the analysis there is need for complex statistical treatment. Of particular interest will be the examination of whether there are combinations of favorable ecologic factors that will outweigh the unfavorable factor of severe malnutrition.

From studies employing the design outlined, greater understanding can emerge of child development in an ecologic setting, but it is necessarily based on inferences from associational analysis. Based on the results, a different kind of research design may then be used to test the causal effects of various combinations of ecologic factors. One such design may be based on an intervention model in which two sets of children from comparable backgrounds would be selected, one set having been malnourished and the other not. The malnourished children and their families would be provided with a set of opportunities for gaining the conditions and experiences shown from the earlier studies to be favorable for functional development. The children who were not malnourished would not receive any special treatment. At various ages the functioning of the children in the two sets would be measured and compared to see if the malnourished children's level of functioning became equal to or higher than that of comparison children. From studies of this kind valuable information could be gained to determine what would be the best forms of intervention to help severely malnourished children to more fully realize their potential functional capacities.

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SUMMARY OF SESSION III

Joaquín Cravioto[1]

After an introduction dealing with the general design of previous investigations, excluding longitudinal ecologic studies, Dr. Richardson qualified them as quasi-experimental in nature and pointed out their limitations. He dwelt on the various types of controls or comparison groups that have been used in different studies, and pointed out that siblings are mainly used not to sort out the genetic component that might be present but rather to provide comparison children whose life experiences are somewhat similar to the malnourished child's. Clearly, only macroenvironmental variables can be reduced by this procedure.

I think we should mention that statistical techniques have recently been used to avoid the need for matched controls. One can use random controls if techniques of covariance analysis are applied. Dr. Richardson gave an example of this approach to illustrate the need for considering the effects of biosocial interaction. This example showed that low birth weight and gestational age have differing consequences for intellectual functioning, depending upon the social class of the child's family. He then proceeded to show us a model for the ecologic study, which I have interpreted as two-phased. The first phase was the identification of the important intervening variables other than malnutrition or nutritional status in some non-intervention studies. Results of this analysis could then be tested by intervention types of research.

In the first part of the model used for non-intervention studies, consideration starts with the question of what are important variables other than nutrition in mental performance or intellectual development. These were derived mainly from the literature about maternal deprivation or environmental deprivation in which important intervening variables were considered. The difficulty of separating different types of variables came out very clearly in the discussion. When one has a chain of events that goes all the way from the society to the individual, such as in the case of mental functioning, it is difficult to know what is an intervening variable and what is the actual etiologic agent.

With an ecologic model, I think that one can get away from this difficulty because if we consider the epidemiologic triad of agent, host, and environment, we do not imply that one of three factors is more important than the other two. For example, malaria can be eradicated by getting rid of swamps, or the mosquito, or the *Plasmodium*, or the sick man. In any case, the chain of events leading to disease would be altered and malaria would disappear. One does not need then to know precisely which is the last link in the chain of events to modify the outcome efficiently.

Dr. Richardson next gave us a very nice example of the different steps involved in the ecologic type of research. These steps begin with the concept, which is then translated into operational definitions, after which the investigator proceeds to the devising of instruments, the testing of the instrument as such, and finally to the proof of the association between what the instrument is gathering and the concept that is supposed to be tapped by the instrument. I think that the last two steps are just a way of rephrasing the classical concepts of reliability and validity of a method.

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There was very little discussion of the outcome variables, but it was pointed out that one has to be careful in choosing them, particularly because of different sensitivities at different times in the life of the individual. Dr. Richardson proposed that once the associations among variables have been identified, a sort of matrix should be analyzed by methods such as multifactorial analysis. I think that if you have defined your questions carefully on reaching the analysis phase, then what sort of statistical technique is used is really a matter of taste. I am not speaking of statistical method, which is part of the design. I mean the statistical technique is factorial or discriminative analysis. It is a matter of choice or a matter of convenience depending on the resources at one's disposal. With the use of factorial analysis one can identify the variables that are so highly correlated among themselves that they actually measure practically the same thing, and separate them from the ones that can be regarded as independent factors.

In the intervention phase of Dr. Richardson's model, one selects some of the variables that earlier studies have indicated are significant. The selection is also guided by the ease of modifying the variable with available resources, particularly staff. One alternative is to proceed to the construction of a theoretical model that will explain the influence of the different sets of variables, either alone or in combination. From this model the quantitative contribution of each variable is theoretically estimated, and the model is tested as a whole if one can devise a common measure that will represent the additive interaction or action of the several variables involved. Alternatively, one could pick certain variables and test them if one wished to determine their specific contribution.

Following the paper there was a discussion of intervention for research and social action to improve the children's mental condition through use of a combination of different variables, including food. Whether intervention should occur in the family, in institutions like schools, or at the community or national level was also debated. This discussion dealt not only with administrative procedures, but also with conception. If a group or a person feels that the highest risk of brain damage is before the age of three years, basing his reasoning on the results of the animal experiments and the inferences he can draw from the circumstantial evidence available about the human, he will have to intervene in the home. If on the other hand he believes that the main damage has not been done by that age, then administrative units such as kindergartens or schools may be the best place for intervention.

Session IV

METHODOLOGIC ISSUES IN MALNUTRITION STUDIES

Chairman

Stephen A. Richardson

Rapporteur

Robert Klein

ISSUES OF DESIGN AND METHOD IN STUDYING THE EFFECTS OF MALNUTRITION ON MENTAL DEVELOPMENT

Herbert G. Birch[1]

Research on the relation of nutritional factors to intelligence and learning has grown extensively in the past decade. Attention has been directed at different components of the combined factors of social disadvantage and poverty in an effort to define reasons for the association of malnutrition with reduced intellectual level. Sociologists, psychologists, and educators have advanced reasons relevant to their particular disciplines for intellectual backwardness and school failure. They have pointed to particular patterns of child care, styles of play, depressed motivation, particular value systems, and deficient educational settings and instruction as factors that contribute to lowered intellectual level and poor academic performance in disadvantaged children. The importance of such variables for achievement cannot be disputed. It would be most unfortunate, however, if in recognizing the importance of these situational components we were to neglect poor nutrition and, in general, defective circumstances in the development of the individual as a biologic organism who interacts with social, cultural, and educational circumstances in the production of dysfunction.

It has long been recognized that the individual's nutrition affects his growth, health, and development. Inadequate nutrition results in stunting, reduced resistance to infectious disease, apathy, and general behavioral unresponsiveness—all factors affecting the child's development and functional capacity. It is therefore essential to explore the relation of nutrition to intelligence and learning ability.

Confusion has resulted from extravagant claims as to the unique contribution of malnutrition to brain impairment and intellectual deficit, as well as from efforts to minimize the importance of nutritional factors and to argue for the primacy of social, genetic, cultural, or familial variables in the production of deficit. Little of use emerges from such controversy. Clearly, malnutrition occurs most frequently in those segments of the population that are economically, socially, and culturally disadvantaged. In discussing lowered intellect in malnourished children from such groups, we must deal with the interaction of nutritional and social or familial factors by considering the possibilities that affected children are dull because they are the offspring of dull parents, or that malnutrition and the general impoverishment of their environments contribute to reducing intellectual function. The task is to disentangle the particular and interactive contributions that different factors make to the development of depressed functional outcomes. The real problem is therefore to define the particular role that nutritional factors may play in the development of malfunction and the interaction of this influence with others that affect the child's development.

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Before considering the ways in which available research permits us to achieve this objective, it is important to clarify the term "malnutrition." When we think of malnutrition our imaginations conjure up images of marasmus and kwashiorkor. These images reflect only the highly visible tip of an iceberg. Intermittent and marginal incomes as well as backward technology result less often in the symptoms characteristic of starvation than what Brock (*19*) has called "dietary subnutrition . . . defined as any impairment of functional efficiency of body systems which can be corrected by better feeding." When present in populations, such subnutrition may be manifested by stunting, disproportion, and a variety of anatomic, physiologic, and behavioral abnormalities (*12*).

Chronic subnutrition is not infrequently accompanied by dramatic manifestations of acute and severe malnutrition in infants and young children. These illnesses, variously reflected in the syndromes of marasmus, kwashiorkor, and marasmic kwashiorkor, may be conditions deriving from acute exacerbations of chronic subnutrition, which in different degrees reflect caloric deficiency, inadequacy of protein in the diet, or both. Acute malnutrition may also be brought about by particular combinations of circumstances such as an episode of malnutrition between past and future courses of relatively adequate nutrition. Studies of children with chronic subnutrition as well as those who recover from acute severe malnutrition provide opportunities to study the effects of nutritional inadequacy on behavioral development.

A number of model systems have been used to explore the relationship of malnutrition to behavior. At the human level these have consisted of (1) comparative studies of segments of well- and poorly-grown children in populations at risk of malnutrition in infancy; (2) retrospective follow-up studies of the antecedent nutritional experiences of well-functioning and poorly-functioning children in such populations; (3) intervention studies in which children in the poor-risk population were selectively supplemented or left unsupplemented during infancy and a comparative evaluation made of functioning in the supplemented, and unsupplemented groups; (4) follow-up studies of patients hospitalized for severe malnutrition in early childhood; and (5) intergenerational studies seeking to relate the degree to which conditions of malnutrition risk in the present generation of children derived from the malnutrition or subnutrition experienced by their mothers when the latter were children.

Studies of humans have been supplemented by a variety of animal models. The available evidence will be considered in relation to these investigative models. Perhaps the most complete study of the relation of growth achievement to neurointegrative competence in children living in an environment of endemic severe malnutrition and chronic subnutrition is a study of rural Guatemalan children (*28*). During their infancy and the preschool years the children lived in a village with a significant incidence of prolonged subnutrition. At school age relatively well-nourished children were identified as the better grown, and children with the highest antecedent risk of exposure to malnutrition identified as those with the lowest growth achievements for age. On the basis of this reasoning two groups of children were chosen from all village children aged six to 11 years. These groups encompassed the tallest and shortest quartiles of height distribution at each age in the total population of village children. To avoid problems associated with the use of intelligence tests as measures of functioning in preindustrial communities, levels of development in the tall and short groups were compared by evaluating intersensory integrative competence through a method developed by Birch and Lefford (*9*).

At all ages taller children exhibited higher levels of neurointegrative competence than did the shorter group. Overall, the shorter children

were two years behind their taller agemates in the competence they showed in processing information across sensory systems.

To control for the possibility that height differences were reflecting differences in antecedent nutritional status rather than familial differences in stature, the child's height was correlated with that of the parents. The resulting correlation was low and insignificant. In contrast, when the same ethnic group lived in more adequate nutritional circumstances the height of children correlated significantly with that of the parents.

Secondly, it was possible that the shorter children in the community at risk as well as in communities not at risk of malnutrition were merely exhibiting generalized developmental lag for both stature and neurointegrative maturation. No differences in neurointegrative competence attached to differences in stature in the children not exposed to endemic malnutrition, however.

Finally, it was possible that the shorter children came from home environments significantly lower in socioeconomic status, housing, and parental education, and that both the malnutrition and the reduced neurointegrative competence stemmed independently from these environmental deficits. When differences in these factors were controlled for they did not erase the differences in intersensory integrative competence between children of different growth achievements for age in the community at nutritional risk.

Over the past several years replications of this study have been conducted in Mexico by Cravioto and DeLicardie (*30*). In addition, Cravioto and his coworkers (*29*) have examined another aspect of neurointegrative competence and auditory-visual integration in Mexican school children. Once again, in children in communities at risk of malnutrition, differences in growth achievement at school age were reflected in differences in auditory-visual integration that favored the taller children. The latter findings are of particular importance because of the demonstrated association between such competence and the ability to acquire primary reading skill (*10, 11, 49*).

A major consideration in interpreting the findings of all these studies is the fact that antecedent malnutrition is being inferred from differences in height rather than by direct observation of dietary intakes during the growing years. A multitude of data from earlier studies, beginning with those of Boas (*16*) on growth differences in successive generations of children of Jewish immigrants and continuing through the work of Boyd Orr (*61*) on secular trends in the height of British children, of Greulich (*40*) on the height of Japanese immigrants, of Mitchell (*58, 59*) on the relation of nutrition to stature, and of Bouterline-Young (*18*) on Italian children, as well as the recent study of heights of 12-year-old Puerto Rican boys in New York City by Abramowicz (*1*), all support the validity of that inference.

Pek Hien Liang and coworkers (*54*) in Indonesia, and Stoch and Smythe (*66, 67*) in South Africa have studied IQ levels in children exposed to chronic subnutrition. In the Indonesian study, 107 children between five and 12 years of age were studied. All came from lower socioeconomic groups. Forty-six of the children had been classified as malnourished during an investigation carried out some years earlier into nutritional status in the area. All children were tested on the Wechsler Intelligence Scale for Children (WISC) and Goodenough tests. The scores showed a clear advantage for the better grown and currently better nourished children. Moreover, the data indicated that the shortest children were markedly overrepresented in the group that had been found malnourished in the earlier survey, and the largest deficits in IQ were found associated with the poorest prior nutritional status.

Stoch and Smythe have carried out a semilongitudinal study of two groups of South African Negro children, one judged in early childhood to be grossly underweight because of malnutrition, and the other considered ade-

quately nourished. At school age, the malnourished children as a group had a mean IQ 22.6 points lower than that of the comparison group. Moreover, these relative differences were sustained through adolescence. Unfortunately, interpretation of the findings in this study is made difficult because the better nourished children came from better families and had a variety of nursery and school experiences the poorly grown children had not shared.

A number of follow-up studies of children severely malnourished in early life have been undertaken. As early as 1960, Waterlow, Cravioto and Stephan (*72*) reported that children who suffered from such severe nutritional illnesses exhibited delays in language acquisition. In Yugoslavia, Cabak and Najdanvic (*20*) compared the IQ levels of children hospitalized for malnutrition at less than 12 months of age with those of healthy children of the same social stratum and reported a reduced IQ in the previously hospitalized group. Of perhaps greater interest was their report of a significant correlation between the severity of the child's illness on admission—as estimated by his deficit in expected weight for age—and IQ depression in the school years. Indian workers (*21*) studied many variables in a group of 19 children who had been hospitalized and treated for kwashiorkor between 18 and 36 months of age. When compared at school age with a well-matched control group, significantly depressed IQ was found in the once severely malnourished children.

To more fully control for differences in the child's family antecedents and microenvironment that may still exist even when more general controls for social class and general circumstances are used in the selection of a comparison group, we (*14, 44*) have compared children malnourished in infancy with their siblings, as well as with children of similar social background. In the first of these studies, intelligence at school age was compared in 37 previously malnourished Mexican children and their siblings. The malnourished children had all been hospitalized for kwashiorkor between the ages of six and 30 months. The siblings had never experienced a bout of severe malnutrition requiring hospitalization. Sibling controls were all within three years of the index patients' age. Full-scale WISC IQ of the index patients was 13 points lower than that of the sibling controls. Verbal and performance differences were of similar magnitude and in the same direction. All differences were significant at less than the 0.01 per cent level of confidence. These findings are in agreement with those of the Yugoslav and Indian workers, and the use of sibling controls removes at least one potential complication for interpretation.

In a second study (*44*), a large sample of 74 Jamaican boys who had been hospitalized for severe malnutrition before they were two years of age were compared with their brothers nearest in age and with their classmates whose birthdate was closest to their own. All children were between six and 11 years of age at follow-up. On examination, neurologic status, intersensory competence, intellectual level, and a variety of language and perceptual and motor abilities were evaluated. Intellectual level was significantly lower in the index children than in either the siblings or the classmate comparison groups. As was to be expected, the order of competence placed the classmate comparison group at the highest level, the index children at the lowest, and the sibs at an intermediate level. The depressed level of the siblings in relation to classmates suggests one disadvantage in sibling studies. Clearly, the presence of a child hospitalized for severe malnutrition may identify a family in which all children are at a high level of risk for significant chronic undernutrition, and the index child may represent an instance of acute exacerbation of this chronic marginal state. Therefore, the index children and sibs can be similar in that they may share a common chronic exposure to subnutrition and differ only in that the index children have experienced a superimposed episode of acute nutritional illness as well. The

use of sibling controls, in any event, does not compare malnourished with nonmalnourished children. Instead, it determines whether siblings who differ in their degree of exposure to acute severe nutritional risk differ in intellectual outcomes.

Other follow-up studies of acutely malnourished children such as those of Cravioto and Robles (*27*) in Mexico, Pollitt and Granoff (*64*) in Peru, Botha-Antoun and coworkers (*17*) in Lebanon, and Chase and Martin (*23*) in Denver, have all been shorter-term follow-ups of cognitive development in younger children.

Cravioto and Robles (*27*) studied the development of returning competence in children hospitalized for malnutrition during their treatment and recovery while in hospital. Their findings, which indicated that behavioral recovery was less complete in the youngest children (hospitalized before six months of age) than in older children, posed the possibility that this earliest period of infancy was the one most critical for insult to developing brain and thus to eventual intellectual outcome. The above-mentioned study of Jamaican children did not yield findings that supported this possibility, however. In that study approximately equal numbers of children who had experienced an acute episode of malnutrition in each of the four semesters of the first two years of life were examined. Equivalent depression of IQ was found to characterize each of the groups when they were separated by age at hospitalization (*44*). One long-term study of sibs and relatives by Hansen (*42*) revealed no differences in IQ between malnourished propositi and sibs. IQ levels at different ages are so markedly discrepant from one another, however, as to make interpretation of his report impossible.

In the Lebanese and Peruvian short-term follow-up studies noted above, depression in intellectual level tended to be found in the index children. In the American study (*23*) and in a Chilean study (*60*), the findings have shown depression in intellectual function in the preschool years in children hospitalized for malnutrition during the first year of life. The American investigators, working in Colorado, found that 20 children who had been hospitalized for malnutrition before the age of one year had a mean developmental quotient on the Yale Revised Developmental Examination 17 points lower than that achieved by a matched control group of children who had not been malnourished. All these studies strongly indicate that severe malnutrition in early life tends to depress later intellectual functioning.

In summary, the follow-up studies of children who have been exposed to hospitalization for a bout of severe acute malnutrition in infancy indicate an association of significant degree between such exposure and reduced intellectual level at school age. The studies, involving social-class controls and sibship comparisons, suggest that it is not merely general environmental deprivation but malnutrition as well that contribute to a depression in intellectual outcome.

The fact of these associations provides strongly suggestive but by no means definitive evidence that malnutrition directly affects intellectual competence. As Cravioto and his coworkers (*28*) have pointed out, at least three possibilities must be considered in the effort to define a causal linkage. The simplest hypothesis would be that malnutrition directly affects intellect by producing central nervous system damage. It may also contribute to intellectual inadequacies as a consequence of the child's loss in learning time when ill, influences of hospitalization, and prolonged reduced responsiveness after recovery. Moreover, it is possible that specific exposures to malnutrition at particular ages may interfere with development at critical points in the child's growth and so create either abnormalities in the sequential emergence of competence or a redirection of development in undesired directions. Although certain of these possibilities (such as hospitalization and postillness opportunities for recovery) can be explored in children, others for

moral and ethical reasons cannot. Thus, it is impermissible to establish appropriate experimental models either for interfering with development at critical periods or for inducing brain damage. The approach to these problems requires either detailed analyses of naturally occurring clinical models or the development of appropriate animal investigations.

Animal models of the effects of malnutrition on brain and behavior have been used to study the issue with a degree of control that is quite impossible in human investigation. A series of pioneering investigations (*31, 32, 74*) have demonstrated that both severe and modest degrees of nutritional deprivation experienced by the animal at a time when its nervous system was developing most rapidly results in reduced brain size and deficient myelination. These deficits are not made up in later life, even when the animal has been placed on an excellent diet after the period of nutritional deprivation.

More recent studies by Zamenhof and coworkers (*79*) and by Winick (*77*) have demonstrated that nutritional deprivation is also accompanied by a reduction in brain cell number. The latter effect has also been demonstrated in the brains of human infants who have died of severe early malnutrition (*78*).

Enzymatic maturation and development in brain is also affected, and Chase and coworkers (*22, 23*) have demonstrated defective enzyme organization in the brains of malnourished organisms.

The evidence in all these studies indicates that the effects of malnutrition vary in accordance with the time in the organism's life at which the deprivation is experienced. In some organisms the effects are most severe if the nutritional insult occurs in the prenatal period when as in others this phenomenon occurs during early postnatal life.

Some confusion in the interpretation of evidence has occurred because of the use of different species, since in different organisms the so-called critical periods occur at different points in the developmental course. In pigs brain growth and differentiation occur most rapidly in the period before birth, whereas in the rat the most rapid growth occurs when the animal is a nursling. In human beings the period of rapid growth is relatively extended and lasts from mid-gestation through the first six to nine months of postnatal life. In man, the brain is adding weight at the rate of 1 to 2 mg/minute at birth and goes from 25 per cent of its adult weight at birth to 70 per cent of its adult weight at one year of age. After that age, growth continues more slowly until final size is achieved. Differentiation as well as growth occur rapidly during the critical periods, with myelination and cellular differentiation tending to parallel changes in size.

Since brain growth in different species occurs at different points in the life course, it is apparent that deprivations experienced at the same chronologic ages and life stages will have different effects in different species. Deprivation during early postnatal life will thus have little or no effect upon brain size and structure in an organism whose brain growth has largely been completed during gestation. Conversely, intrauterine malnutrition is likely to have only trivial effects on the growth of the brain in species in which the most rapid period of brain development occurs postnatally. When these factors are taken into account, the data leave no doubt that the coincidence of malnutrition with rapid brain growth results in decreased brain size and in altered brain composition.

It would be unfortunate if brain growth in terms of cell number were to be viewed as the only definer of rapid change and thus of critical periodicity. In the human infant neuronal cell number is probably largely defined before the end of intrauterine life. Thereafter, through the first nine months of postnatal life, cell replication is that of glial cells, a process that terminates by the end of the first year. Myelination continues for many years thereafter, however, as does the proliferation of dendrite branchings and other features of brain organi-

zation. It is most probable, therefore, that in man the period of vulnerability extends well beyond the first year of life and into the preschool period. Such a position is supported by the findings of Champakam and coworkers (*21*), who it will be recalled, found significant effects on intellect in their group of malnourished children who had experienced severe malnutrition when they were between 18 and 36 months of age.

Other workers who have used animal models have sought to study the effects of malnutrition on behavioral outcomes rather than on brain structure and biochemical organization. The typical design of these studies has been investigations in which animals have been raised on diets inadequate in certain food substances or in which general caloric intake has been reduced without an alteration in the quality of the nutriments. Such animals have then been compared with normally nourished members of the species as to maze learning, avoidance conditioning, and open field behavior. Unfortunately, most of the investigations have suffered from one or another defect in design that makes it difficult to interpret the findings. Though in general the nutritionally deprived organisms have tended to be disadvantaged as learners, it is not at all clear whether this is the result of their food lacks at critical points in development or whether the differences observed stem from the different handling, caging, and litter experiences to which the well and poorly nourished animals were exposed. In a considerable number of studies, however, food or avoidance motivation have been used as the reinforcers of learning. There is abundant evidence (*6, 37, 52, 56*) that nutritional deficiency in early life affects later feeding behavior. Consequently, it is difficult to know whether the early deprivation has affected food motivation or whether it has affected learning capacity. The use of learning situations that do not involve food but are based upon aversive reinforcement do not remove interpretative difficulties since early malnutrition modifies sensitivity to such negative stimuli (*53*).

One must recognize that although the animal evidence suggests that early malnutrition may influence later learning and behavior, it too is by no means conclusive. Moreover, when learning has been deleteriously affected, the mechanism through which this effect has been mediated is by no means clear. What is required is a systematic series of experiments in which behavioral effects are more clearly defined, and in which the use of proper experimental designs, accompanied by appropriate controls, permits the nature of the mechanisms affected to be better delineated.

Thus far, in our discussion of both the human and animal evidence, we have been considering the direct effects of nutritional deprivation on the developing organism. This is clearly too limited a consideration of the problem. It has long been known (*61*) that nutritional influences may be intergenerational and that an individual's growth and functional capacity may be affected by the growth experiences and nutrition of his mother. In particular, the nutritional history of the mother and its effect upon her growth may significantly affect her competence as a reproducer. In turn, this reproductive inadequacy may affect the intrauterine and birth experiences of the offspring.

Bernard (*8*) has clearly demonstrated the association between a woman's nutritional history and her pelvic type. He compared one group of stunted women in Aberdeen, Scotland, with well-grown women and found that 34 per cent of the shorter women had abnormal pelvic shapes that were conducive to disordered pregnancy and delivery as compared to 7 per cent of the well-grown women. Greulich and coworkers (*39*) had reported still earlier that the rounded or long oval pelvis, which appears to be functionally superior for childbearing, was more common in well off, well-grown women than in poorer clinic patients. They further noted, as had Bernard, that these pelvic abnormalities were strongly associated with shortness.

Sir Dugald Baird and his colleagues in Aberdeen, Scotland, have conducted a continuing series of studies from 1947 onward on the total population of births in that city of 200,000 to define the patterns of biologic and social interactions that contribute to a woman's growth attainments and to her functional competence in childbearing. Baird (*2*) noted more than 20 years ago that short stature, which was five times as common among lower-class than among upper-class women, was associated with reproductive complications. He pointed out (*3*), on the basis of analyzing the reproductive performances of more than 13,000 first-delivery women, that fetal mortality rates were more than twice as high in women who were under five feet one inch in height than in women whose height was five feet four inches or more. Baird and Illsley (*4*) demonstrated that premature births were almost twice as common in the shorter as in the taller group. Thomson (*68*) extended these observations by analyzing the relation between maternal physique and reproductive complications in the more than 26,000 births that had occurred in Aberdeen over a 10-year period and found that short stature in the mother was strongly associated with high rates of prematurity, delivery complications, and perinatal deaths at each parity and age level. He concluded that "it is evident that whatever the nature of the delivery the fetus of a short woman has less vitality and is less likely to be well-grown and to survive than that of a tall woman."

It was of course possible that these findings simply reflected differences in social-class composition of short and tall women, and were based upon differences in "genetic pool" rather than in stunting as such. To test this hypothesis, the Aberdeen workers (*5*) reexamined their data for perinatal mortality and prematurity rates by height within each of the social classes for all Aberdeen births occurring in the 10-year period from 1948 to 1957. They found in every social class that shortness was associated with elevated rates of both prematurity and perinatal deaths. Concerned that the findings in Aberdeen might not be representative, they also analyzed the data from the all-Britain perinatal mortality survey of 1958 and confirmed their findings. Moreover, Thomson and Billewicz (*69*) in Hong Kong and Baird (*5*) have substantiated the Aberdeen findings for Chinese and West African women, respectively. Other findings in a similar vein from this series have been summarized by Illsley (*47*).

The available data therefore suggest that women who are not well-grown have characteristics that negatively affect them as childbearers. In particular, short stature is associated with pregnancy and delivery complications and with prematurity. Since growth achievement within ethnic groups is a function of health history and in particular nutrition, it is clear that the mother's antecedent nutritional history when she herself was a child can and does significantly influence the intrauterine growth, development, and vitality of her child. Moreover, a mother's inadequate nutritional background places her child at elevated risk of damage at delivery.

It is instructive to consider the consequences for mental development and learning failure that attach to the most frequently occurring consequence of poor maternal growth—low birth weight. Concern about the consequences of this condition is hardly new. Shakespeare indicated it as one of the peculiarities of Richard III, and Little (*55*) linked it with the disorder we now call cerebral palsy. Benton (*7*) reviewed the literature up to 1940 and found that, though most students of the problem maintained that prematurity was a risk to later mental development, others could find no negative consequence attaching to it. At that time no resolution of the disagreement could be made because most of the early studies had been carried out with serious deficiencies in design and techniques of behavioral evaluation. Infants of low birth weight or early in gestational age were often compared with term

infants who differed from them in social circumstances as well as in perinatal status. Estimates of intellectual level were made with poor instruments and often depended on "clinical impression" or testimony from parents or teachers.

Serious and detailed consideration of the consequences of low birth weight for later behavior can properly be said to have begun with Pasamanick, Knobloch, and their colleagues shortly after World War II. These workers were guided by a concept they referred to as a "continuum of reproductive casualty." They argued that there was a set of pregnancy and delivery complications that resulted in death through brain damage, and hypothesized that in infants who survived exposure to these risks "there must remain a fraction so injured who do not die, but depending on the degree and location of trauma, go on to develop a series of disorders extending from cerebral palsy, epilepsy and mental deficiency, through all types of behavioral and learning disabilities, resulting from lesser degrees of damage sufficient to disorganize behavioral development and lower thresholds to stress" (*62*). In a series of retrospective studies these investigators identified prematurity and low birth weight as being among the conditions most frequently associated with defective behavioral outcomes. They therefore undertook a prospective study of a balanced sample of 500 premature infants born in Baltimore in 1952 and compared them with term control infants born in the same hospitals who were matched with the prematures for race, maternal age, parity, season of birth, and socioeconomic status (*50*). Four hundred pairs of cases and controls were still available for study when the children were between six and seven years of age, and examination of the sample indicated that at this age the prematures and term children continued to be matched for maternal and social attributes (*75*). Findings at various ages persistently showed the prematures to be less intellectually competent than the controls. At ages three to five the prematures were relatively retarded intellectually and physically, and had a higher frequency of definable neurologic abnormalities (*43*, *51*). At ages six through seven IQ scores on the Stanford-Binet test were obtained, as were WISC IQs at ages eight to nine. At both age levels lower birth weights were associated with lower IQs (*75*, *76*).

Although certain British studies such as that of McDonald (*57*) and of Douglas (*33*, *34*) appear to differ somewhat from these findings, reanalysis of their data (*12*) indicates a similar trend. More dramatic differences between prematures and term infants have been reported by Drillien (*35*, *36*), but interpretation of her data is made difficult by complexities in the selection of the sample studied.

A number of analyses suggest that the effects of prematurity are not the same in different social classes. Children from the lowest social classes appear to have subsequent IQ and school performances more significantly depressed by low birth weight than is the case with infants in superior social circumstances. This has been reported for Aberdeen births (*46*, *65*) and for Hawaiian children in the Kauai pregnancy study of Werner (*73*). There appears to be an interaction between birth weight and family social condition in affecting intellectual outcome, but the precise mechanisms involved in this interaction are as yet unclear.

If the risk of deficient intellectual outcome in prematurity is greatest for those children who are socially disadvantaged as well, our concern in the United States with the phenomenon of prematurity must increase. In 1962, more than 19 per cent of nonwhite babies born in New York City had a gestational age of less than 36 weeks as compared to 9.5 per cent of white babies, and in Baltimore this comparison was 25.3 per cent in nonwhite infants as compared to 10.3 per cent in whites (*70*). In 1967, nationally, 13.6 per cent of nonwhite infants weighed less than 2,500 g as compared to 7.1 per cent of white infants (*71*). Other relevant and more detailed analy-

ses of the social distribution of low birth weight and gestational age on both national and regional bases, together with an analysis of their secular trends, provide additional support for these relationships (*12*). Thus, low birth weight is most frequent in the very groups in which its depressing effects on intelligence are likely to be.

On the basis of the evidence so far set forth, it may be argued with considerable justification that one can reasonably construct a chain of consequences starting from the malnutrition of the mother when she was a child, to her stunting, to her reduced efficiency as a reproducer, to intrauterine and perinatal risk to the child, and to his subsequent reduction in functional adaptive capacity. Animal models have been constructed to test the hypotheses implied in this chain of associations, most particularly by Chow and his colleagues (*24, 45*) and by Cowley and Griesel (*25, 26*). The findings from these studies indicate that second and later generation animals who derive from mothers who were nutritionally disadvantaged when young, are themselves less well-grown and behaviorally less competent than animals of the same strain deriving from normal mothers. Moreover, the condition of the offspring is worsened if nutritional insult in its own life is superimposed on early maternal malnutrition.

A variety of factors would lead us to focus on the last month of intrauterine life as one of the "critical" periods for the growth and development of the central nervous system in humans. Both brain and body growth, together with differentiation, occur at a particularly rapid rate at this time. It has been argued, therefore, that whereas marginal maternal nutritional resources may be sufficiently adequate to sustain life and growth during the earlier periods of pregnancy, the needs of the rapidly growing infant in the last trimester of intrauterine existence may outstrip maternal supplies. The work of Gruenwald and coworkers (*41*), among other research, suggests that maternal conditions during this period of the infant's development are probably the ones that contribute most influentially to low birth weight and prematurity. Such concerns have led to inquiries into the relation of the mother's nutritional status in pregnancy to the growth and development of her child. In considering this question, it is well to recognize that as yet we have no definite answer to the question of the degree to which maternal nutrition during pregnancy contributes to pregnancy outcome. Clearly, whether or not nutritional lacks experienced by the mother during pregnancy will affect fetal growth is dependent upon the size and physical resources of the mother herself. Well-grown women are most likely to have tissue reserves that can be diverted to meet the nutritional needs of the fetus, even when pregnancy is accompanied by significant degrees of contemporary undernutrition. Conversely, under the same set of circumstances poorly grown women with minimal tissue reserves could not be expected to provide adequately for the growing infant.

The data presented reveal that the behavioral outcomes attaching to malnutrition are at every point the product of both the nutritional circumstances and the general environments in which children grow and develop. Investigators, many of whom have been fully aware of the varied features of environment that are simultaneously present and capable of affecting children who have experienced malnutrition, have tended to use an additive model for the attribution of cause. They have argued that the variance in behavior outcomes may be viewed as the sum of the variances that are produced by nutritional and nonnutritional factors. Expressed formally, such an additive model is,

$$\sigma^2_b = \sigma^2_N + \sigma^2_{NN}.$$

In such a standard additive model each component can be fractionated into subcomponents, such as kinds of behavior, kinds of nutritional

factors, and types of nonnutritional components.

Such a model is possibly true, however, only if we assume we are dealing with a quasi-experimental situation and if we ignore both correlations and interactions between nutritional and nonnutritional influences. This can in fact be done in experimental situations in which randomization of both nutritional and nonnutritional components is possible. In field studies in which such randomization is patently impossible, the model becomes grossly inadequate.

Malnutrition is not randomly distributed with respect to nonnutritional factors. Rather, malnutrition occurs most frequently in certain kinds of families and environments and least frequently in others. A strong correlation consequently exists between nutritional and nonnutritional components. Our formula therefore must be corrected to include a consideration of this correlation. The correction factor could be expressed as,

$$(K)r_{N.\,NN}\,\sigma_N\,\sigma_{NN}.$$

This correction factor takes into account the correlative relations between nutritional and nonnutritional components.

In addition, the consequences of malnutrition are not separable from the nonnutritional circumstances in which the malnourished individual is developing. As Richardson pointed out in his paper at this conference, an interaction exists whereby the consequences of malnutrition for children living in good environments are distinctly different from the contribution malnutrition makes to development of children in poor ones. Consequently, we must introduce a second correction factor in our model, one for the interaction between nutritional and nonnutritional components. This may be expressed as, (f) N.NN.

Our revised model, therefore, now has the following form,

$$\sigma^2_b = \sigma^2_N + \sigma^2_{NN} + (K)r_{N.\,NN}\,\sigma_N\,\sigma_{NN} + (f)\,N \cdot_{NN}.$$

Such a model reflects the ecologic requirements and indicates further research needed to solve the problem of the effects of malnutrition in a representative sampling of environments. It is not fundamentally different from biometric models applicable to genetic data (*48*).

A second methodologic question also requires some note. This is the fact that various investigators have studied children exposed to malnutrition at different points in their developmental course. Clearly, effects may or may not be manifest at particular age levels, not only for nutritional and nonnutritional factors but even for genetic influences. A recent report by El-Oksh and coworkers (*38*) illustrates this point.

A parallel situation with regard to the genetic determination of body weight in mice (*38*) illustrates the point under consideration. The results of partitioning phenotypic variation of weight at different ages into components are shown in Table 1:

Table 1. Phenotypic weight variation.

Age in weeks	Genetic (heritability)	Maternal		Residual (environmental)
		Prenatal	Postnatal	
0	0.00	0.52	−0.14	0.62
1	0.11	0.27	0.30	0.31
2	0.23	0.25	0.38	0.14
3	0.30	0.12	0.30	0.29
6	0.26	0.17	0.23	0.34

As may be clearly seen, birth weight is independent of genotype of the young and is largely determined by prenatal effects exercised by the dam. Their significance gradually decreases while postnatal maternal effects and the genotype of the offspring begin to play an increasingly important role. After weaning at three weeks of age, the maternal effects begin to drop off.

If we take these genetic findings seriously and apply their lesson to the study of malnutrition, what is required is a consideration of outcomes over a wide range of ages from the

immediately postacute period of malnutrition to late adult life.

These models and considerations make apparent the incompleteness of our present knowledge and, it is to be hoped, define opportunities for further investigation.

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SUMMARY OF SESSION IV

Robert E. Klein[1]

Dr. Birch addressed himself to two general areas, the methodologic problems encountered in human studies of the effect of malnutrition on later intellectual development, and animal experiments and their utility in the study of behavioral outcomes following nutritional insult.

Dr. Birch noted that, although the extant data and the published literature indicate long-lasting effects on behavior and performance (in terms of IQ and achievement measures) following malnutrition, there are serious methodologic problems in most studies. Much of this methodologic grief stems from the fact that malnutrition is not randomly distributed in the general population. Thus, simple nonecologic models, which merely sum the environmental and nutritional effects, are inappropriate.

Dr. Birch then discussed a simple interaction model that would allow the investigator to examine the effects of nutritional insult at various levels of nonnutritional factors. He buttressed his case for the need to use interactive models by pointing out that we must have a longitudinal focus in this type of study, since at distinct developmental stages genetic characteristics may interact with the type of behavior being examined so that the simple two-way matrices (although interactive) really require a third, longitudinal-developmental dimension. I see this as an extremely useful way to look at the problem and, once published and disseminated, it should aid investigators in avoiding the pitfalls that have characterized much of the published research in this area.

In discussing the use of animal models in the study of malnutrition and its effects on human behavioral development, Dr. Birch identified three important advantages: tight—e.g., genetic—control, random assignment of subjects to experimental treatments, and the availability of objective tests and outcome measures by which the effects of nutritional insult can be evaluated.

The discussion of animal experiments dwelt on two issues, the sensitivity of behavioral measures and the interpretation of results. On the issue of sensitive behavioral measures, Dr. Birch referred to Karl Lashley's work as an example of how one might use damaged animals to search for evaluation procedures sensitive to different levels of nutritional insult. His major points were that there are different levels of complexity in behavior and that the evaluative technique must focus on the desired level of behavioral complexity.

The focus on sensitive behavioral measures in animal research remains an important point. Discussion of this issue was obscured because of the use of Lashley's work as an example. Dr. Dobbing pointed out that it is inappropriate to use ablation as an example of CNS insult in nutritional research, since nutritional insult frequently occurs early, and the ablation example does not come to grips with the concept of plasticity in central nervous system development and behavior. I believe Dr. Birch did himself a disservice by using Lashley's work as an example, because it was clear throughout his presentation that both developmental differences and the point in development at which evaluation is attempted are important considerations.

In conclusion, Dr. Birch pointed out that even after sensitive measures have been developed and successfully applied, additional experimental probes are frequently necessary

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because constructs encountered in the literature (e.g., "motivational differences") are often descriptive rather than explanatory and have little or no predictive power.

In the discussion following Dr. Birch's paper, Dr. Winick disputed the contention that little longitudinal animal research had been accomplished. He noted research in developmental biochemistry as an example. A discussion of how to define "longitudinal" research followed, and this discussion more or less died instead of being successfully resolved.

Dr. Stewart discussed his research with dogs. After a careful and considered longitudinal investigation, he gave up the study because he felt it was relatively difficult to translate and extend the findings to human behavior. He felt in general that the scientific community was uninterested in these results and that one could only talk about differences in behavior, since there is relatively little to say about why the differences occur and what they mean with respect to human behavior.

No general agreement was reached about extrapolating results from animal behavior studies to human behavior.

Session V

FUTURE RESEARCH DIRECTIONS

Chairman

David Picou

Rapporteur

Herbert G. Birch

SUMMARY OF SESSION V

Herbert G. Birch[1]

Dr. Picou opened the session by asking us to address ourselves to two issues: first, What are more specific, revealing, and feasible studies that need to be conducted?, and second, What are potential areas for conceptual as well as experimental and observational consideration? For example, what is the relevance of animal models to the human condition? What kinds of tools are required for better studies of young children? What are the potential contributions of intervention studies, and what kinds of intervention studies are needed? To what degree are there important areas of research that have been ignored or relatively neglected, e.g., prenatal malnutrition? How good is the evidence with respect to the permanence or transience of nutritional effects on brain and behavior? And, finally, do we have any systematic information on the relation of recovery rates during severe nutritional illness to the permanence or transience of effects.

In general, the first part of the discussion concerned itself with the issue, Have we reached the point in investigation where further research is relatively uninformative with respect to certain main questions? These "main questions" were identified as: Does malnutrition have an effect on brain and behavior? Do we know what needs to be done to prevent this? What kinds of information are valuable for answering these questions?

The second half of the discussion focused on the design of research. Consideration of a series of models made it clear that there were several levels at which research took place. One of these was a general descriptive level, namely a consideration of whether there are consequences, and whether such consequences are relatively permanent and quantifiable or measurable in any way. Second, there was the issue of the functional consequences of the structural, biochemical, and physiologic alterations that had been reported. Third, there was the level of the general contribution to science that concern with the problems of malnutrition makes.

In this connection it was noted that the study of malnutrition or of the nutritional requirements for growth and development represents strategic paths of entry into the general questions of developmental biology, and into a consideration of questions relevant to the growth and organization of functional systems in developing individuals. Such concern leads to the level of biologic mechanism and to a consideration of cellular and subcellular processes in development. Finally, it was pointed out that at a biosocial level we must deal with the relevance of any of these studies to the human condition, and to general social policy. It was agreed, however, that this issue would be deferred for discussion in the last session.

In the course of considering animal investigations, one point in particular was made on several occasions and needs underscoring. It was noted that in animal investigations there has been a focused concern upon brain and its organization, and relatively insufficient relation of changes in brain to the general bodily environment in which the changes exist. This was a point made by Drs. Dobbing, Cheek, Stewart, and others. They emphasized that we know little about the associations between the kinds of changes that are registered in brain physiology, and the kinds of changes that may simultaneously be occurring in the rest of the body and which may be as important as the

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environment of brain. Particular emphasis was placed upon our lack of knowledge of endocrine organization as it may contribute to the physiology of the brain, and to its alteration, permanent or otherwise, in malnutrition.

There is a large body of data which indicates that under a variety of conditions of stress there are alterations in endocrine organization on a relatively permanent basis. Moreover, in terms of a neuroendocrine model these alterations are important for the adaptive capacities of organisms and their behavior. Consequently, a renewed concern with the general physiologic consequences of malnutrition represents a more expanded path for dealing with behavior changes than the simplistic one of brain damage, e.g., brain is damaged, behavior is altered.

Several problems with respect to the human condition were also brought forward. The first deals with the degree to which nutritional and nonnutritional components interact in the production of behavioral sequelae. Various people said that we did have enough evidence to indicate that relatively permanent changes in brain derive from malnutrition. Others stated with equal firmness that this question was not yet answered.

It is clear that we have a huge body of evidence indicating that depressed levels of functioning are associated both with malnutrition and more generally with conditions of social and stimulational disadvantage that characterize the life styles of families in which malnutrition occurs. What is clear is that repetitious investigation of this phenomenon is not productive, and that what is needed is the application of new models appropriate for the study of biosocial interactions in the problem. Such models have been proposed in the meeting, and may be used as a basis for subsequent inquiry. Clearly, we must move to a new level of concern with the problem, rather than with the restatement of the older question that dominated the beginning of the meeting.

The second issue was the relation of physiologic recovery to recovery of behavioral functions. We have relatively sparse information on recovery states during acute severe malnutrition, and on the relation of physical and physiologic recovery at that point in time to behavioral recovery. Preliminary studies such as those carried out by Cravioto and Robles in Mexico and some information available from D. S. McLaren (private communication) in Lebanon suggest that some association exists between rates of physiologic and behavioral recovery. These data are difficult to interpret because of the small number of cases and because of certain other difficulties in design, namely, insufficient specification with respect to the chronicity or acuteness of the illness, insufficient specification with respect to the age of malnutrition, and the like. It is clear from these gaps in our information that studies of recovery states and of the relation between physical, physiologic, and behavioral phenomena are very much to be desired. Further, we have no systematic evidence on the long-term relationship between behavioral recovery during acute illness and later functioning. Such questions are raised as issues for further and productive research.

A somewhat related question is whether the method of malnutrition treatment in any degree affects the nature of the outcome. We have not had any systematic consideration of the relation of different kinds of treatment—of different combinations of physiologic, physical, and behavioral rehabilitative procedures—to the ways in which outcome may be affected. McLaren in Beirut has begun such an inquiry. On the basis of the partial information we have about that study, it is indeed an area that appears profitable for further work. These workers suggest that real differences in both the rate at which children recover physically from the illness and in behavioral recovery rates occur when stimulation at the play level is introduced into hospital care. These data must still be related to age at malnutrition and severity and duration of the illness.

In the discussion it was noted that we have little information about the present and background history, health conditions, and circumstances of individuals as they relate to whether or not they become severely malnourished, and to whether or not such malnutrition as they may experience is expressed in permanent or transient depressions of behavioral competence. There is need for certain kinds of long-term follow-up and of longitudinal studies.

A further question that could productively be explored was that of the time in development at which defective or deficient outcomes become manifest and the kinds of behavioral change or alteration that are exhibited at such points in time. For example, a language deficit is unlikely to be manifest in the first year of life, but may be manifest later. More importantly, it may well be that particular features of behavior, and adaptation and resistance to stress may not manifest themselves, except as sleeper effects much later than the time of insult and illness itself. What was suggested in the discussion was that we pursue far more long-term follow-up studies of stress into later life. Dr. Fred Richardson argued that it was important for us to shift from consideration of this issue as purely a pediatric problem to one relating to adult functioning as well, including geriatric functioning. This aspect of the issue has indeed occupied a most prominent place in studies of overnutrition, but has not constituted a serious realm of inquiry in the areas of undernutrition or malnutrition. Studies of overnourishment might benefit from investment in comparative studies of undernourished adult populations. Questions that might be posed are: How does the incidence of atherosclerosis differ in undernourished versus overnourished populations? Does premature senility occur in adults who have suffered either chronic lifelong undernutrition (or overnutrition), or prolonged severe malnutrition, as in wartime concentration camps?

Finally, it was pointed out that a considerable need exists for defining types and times of intervention and types and styles of effective procedures for preventing malnutrition. In particular, it was emphasized that we needed to know a good deal more about nutritional attitudes and practices and the ways in which food use and a specific application to members of family groups is reflected in the behaviors, attitude structures, and cultures of the communities in which man lives. These general considerations were followed up by the statement of a series of explicit researches that various members of the seminar felt they wanted to undertake in the near future. These studies include: (1) an emphasis on reexamining new models for considering the interaction of nutritional and nonnutritional factors; (2) a focus upon early development and cognitive consequences as they may reflect modifications in developmental course and process in relation to malnutrition; (3) emphasis on a detailed consideration of maternal malnutrition; (4) consideration in detail of prenatal malnutrition and its interaction with the nutritional circumstances in postnatal life; (5) study of the intergenerational effects and chronicity of subnutrition and its consequences for development; and (6) a wish to define limits during recovery courses in which full or relatively full recovery of physiologic and anatomic as well as biochemical and behavioral function might be possible.

Session VI

SOCIAL AND ADMINISTRATIVE PROBLEMS

Chairman

D. B. Jelliffe

Rapporteur

Robert Cook

NUTRITION, PUBLIC HEALTH, AND EDUCATION

Jack Tizard[1]

As scientists concerned with the long-term effects of malnutrition in early life, we should consider ways in which our knowledge can be utilized by those responsible for social, educational, and public health policy, but as a group we are not particularly well qualified to give advice on nutrition policy to governments or public administrators. Economists, anthropologists and sociologists, agriculturalists and political scientists, and other biologic and social scientists may have a more direct part to play as consultants to governments than those whose primary concern is biology and psychology as related to pathology. But we must try to answer two questions: What use can be made of *our* knowledge?, and, What steps should we as scientists take to ensure that full use is indeed made of it?

The classical view of science's social implications—that science is an activity that is essentially a search for truth unsullied by considerations of utility—is not likely to be widely held by scientists. For Rutherford, as for most of his colleagues and students, part of the satisfaction to be derived from the study of subatomic physics lay in the belief that theory and discovery in this field had no practical consequences. Knowledge was pursued for its own sake. Scientists and public alike agreed that the pure scientist was not responsible for the use of discoveries that he as pure scientist did not exploit for personal gain himself.

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In 1945 this understanding between scientists and the public, which was already under strain, was destroyed by the atomic bomb. The full effects of the bomb were not immediately apparent, however, in that after World War II pure science prospered as never before. In Britain as in other advanced countries, it has been among the most rapidly growing of the major industries and support for it has continued to be given with surprisingly few strings. Pure science, no less than the exploitation of scientific discovery for practical, commercial, and military purposes, has been a major beneficiary of the affluent society.

This golden era for science is almost certainly passing. In an age that is increasingly disillusioned and afraid of the consequences of scientific discovery for society, the public is beginning to demand that some priority be given to scientific research that is relevant to the human condition, that is, capable of being used directly for human betterment. Scientists have rightly pointed out, of course, that research often has unanticipated consequences for good as well as for ill, and they have argued that a direct attack on major social problems is often useless. Their argument is incontrovertible, but the public remains unconvinced and uneasy. Furthermore, scientists themselves appear increasingly to believe that the distinction between "pure" and "applied" science has all along been nothing more than a convenient fiction. Thus the pure scientist no less than the applied one is likely today to be concerned

with the social responsibility of scientists, and those who deny that scientists have such a responsibility find their views increasingly regarded as old-fashioned.

Because biologic scientists have always had a close association with medicine, the notion of social responsibility is one that has been easier for them to accept than for their colleagues in the physical sciences. Where does it take us in regard to research on the effects of malnutrition?

The Application of Research Findings in Nutrition

There is a wide range of attitudes among those who work in the field of nutrition and accept the view that the scientist cannot be absolved of responsibility for his findings. Some maintain that our knowledge today is too slight to enable us to offer any advice whatsoever to those who make public policy. Their argument is that the realities of undernutrition are exceedingly complex and only imperfectly comprehended, and that before we speak at all about them we must do much more research to elucidate basic mechanisms and to judge the relative importance of nutritional and other factors in mental and physical development. A not dissimilar consequence follows from the view of others who at first sight appear to think the opposite. To them our knowledge is so great that no self-respecting scientist can in good faith endorse the "simplistic" solutions likely to appeal to a politician. Since whatever he says will be misconstrued, runs this argument, the best thing the scientist can do is to mind his own business. A third view, more commonly expressed by social than by medical scientists, may be described as utopian or millennial. It holds that unless a "total" change is made in the structure of society, any piecemeal reform is mere tinkering. The scientist can thus show his social concern most effectively by abandoning science for politics. A quite different view is propounded by others who offer one or another panacea (breast feeding is the current favorite) that they believe will largely solve the major complex problems of malnutrition and undernutrition.

All these schools of thought in their different ways counsel inactivity on the part of the scientist. He does not know enough or he knows too much to offer advice. The problem is insoluble without revolution, or the solution is simple and is already at hand so that only propaganda is required to implement it. The difficulties are "fundamentally" educational, or they are economic; they are psychologic, having to do with attitudes toward food or child-rearing practices, or they are "primarily" genetic, being perpetuated by succeeding generations of poor, ignorant, feckless, and stupid people who share a common heredity drawn from a stagnant pool; the problems are largely administrative; they are physical; they are merely statistical artifacts; they are and have been since the time of Malthus the major problems that have confronted the world.

The attitude most of us concerned with nutrition would probably hold is that while the problems are indeed complex and little understood in detail, we already know enough to advise that some forms of political action be undertaken and others not. The situation is similar to that in the nineteenth century in which various public health problems were effectively tackled long before their causes were understood or specific forms of treatment were available. Mental retardation presents a similar situation today: it is a problem no less complex than malnutrition, but one to which scientists have made major social contributions. Through epidemiologic inquiry they have charted the frequency, severity, and prognosis of mental retardation, have investigated forms of treatment and training, have calculated the social and administrative facilities that society requires to deal with the mentally retarded, and have given estimates of the financial and social costs of doing so. It is abundantly clear that left to themselves, adminis-

trators charged with making policy about the mentally handicapped would be likely to cling to traditional wisdom. Radical changes in social policy in this field have come because people outside the system have provided leads toward fresh ways of doing things. The same may apply in the field of nutrition.

I suggest that there are three ways the scientist as scientist (as opposed to politician or citizen) can make a contribution to social policy on nutrition. First, he can provide expert factual information together with an informed opinion based upon his knowledge; second, he can assist in the utilization of his findings by making them readily available, or by adding an explicitly practical component to an ongoing research project; third, he can aid in the design and evaluation of "action" projects to try out different ways of doing things.

The Provision of Material and Advice

Malnutrition and undernutrition are public health problems whose study can be effectively carried out using epidemiologic methods. The surveys described at this seminar indicate that epidemiologic and clinical research is already highly productive. Anthropometric measures enable us to obtain valid estimates of the prevalence of undernutrition in various populations, and for particular purposes they may be supplemented by biochemical and clinical measures. Surveys carried out of properly selected samples can thus provide both adequate measures of the extent of undernutrition in specific populations and markers against which to judge the success of changes in nutritional policies. As a complement, dietary surveys including investigations of the prevalence and consequences of various food taboos and preferences can give a picture of current eating habits in populations and subgroups, while more global surveys of food supplies and food consumption present crude national or regional estimates of the amount of food available.

It is well recognized that figures on child mortality can be used to monitor changes in the health of the population and to highlight differences between one population and another. In Jamaica in 1965, for example, the mortality rate among children aged six to 24 months was more than eight times that in England and Wales (6). Differences in mortality were much less in other groups of children under the age of five years. The period of six months to two years may be seen from these data to be a particularly vulnerable and critical one for the Jamaican child. Among children aged 12 to 23 months, malnutrition was the greatest single recorded cause of death in Jamaica in 1963, followed by gastroenteritis and pneumonia. Population mortality statistics and hospital admission and mortality statistics indicate both the relative importance of various diseases and the age groups that are particularly susceptible to severe illnesses of various sorts. Epidemiologists may be primarily interested in such data for other reasons, but the point is that the data themselves can be used to monitor the health of a people.

Epidemiology is of course that branch of medicine which is particularly closely related to health service planning. In a more general sense, reviews of current knowledge that include a consideration of social implications also serve an invaluable function in directing attention to matters otherwise likely to be known only in shadowy outline and by a small group of specialists. Boyd Orr did this for nutrition in the 1930's, and in different ways the 1967 International Conference on Malnutrition, Learning, and Behavior (3) and the volume *Disadvantaged Children* by Birch and Gussow (1) opened up whole areas of knowledge to the educated public as well as specialists.

Just as reviews are required to direct the attention even of specialists to a field's state of knowledge and its social implications, however, so further popularization is likely to be required to make the public aware that a problem exists. Furthermore, most academic research cannot or will not be assimilated by professional practitioners unless it is reformulated so as to

be relevant to the problems that concern them. This is not likely to happen unless research findings are presented and interpreted for specific audiences, with specific and practical objectives in mind. A recent discussion concerned with dissemination of social science research findings (4) distinguished five different types of target audience, each requiring a different approach and possibly a different vehicle of communication: academics, social scientist practitioners outside the academic world, practitioners in other disciplines, practicing managers and administrators (and presumably politicians), and the general public. In the field of nutrition the list of target audiences would be different but equally diverse.

Of all target audiences, government is perhaps the most important and most difficult to reach. The recent Waterlow Report prepared by the Nutrition Advisory Committee of the Scientific Research Council of Jamaica on nutrition in Jamaica (6) provides a model showing how scientists can use their knowledge to make recommendations for public policy. The Report, which has not yet been published,[1] was concerned with long- and short-term policy toward nutrition, its economic and sociologic implications, and trends, new developments, and education in nutrition. It dealt specifically with the situation in Jamaica, but its approach is generally valid; it can serve as a model for research workers in other countries who wish to show the policy implications of current knowledge.

One feature of the Waterlow Report (and this is likely to apply also in other countries) was that it compiled a great deal of available but not readily accessible information on various aspects of nutrition in Jamaica that had not previously been pieced together in any systematic way. Hence a factual document that connected and collated in an easily available form the scattered literature on Jamaican nutrition is likely to be useful for reference and as a baseline for future studies and surveys. The Nutrition Advisory Committee also thought it desirable to discuss explicitly the implications of its findings and in doing so it was faced with a dilemma:

> On the one hand it is desirable that technical and professional people should give advice which is realistic and practical in the light of the situation which exists. It is not helpful to make sweeping and generalised proposals which cannot be carried out in a country with limited resources. On the other hand, we would be failing in our duty if we did not propose measures which seem necessary to improve the health and wellbeing of the people, simply because they will draw upon money and personnel which are in short supply. We realise fully that for government all action and expenditure are a matter of priorities. We have therefore attempted to maintain a balance between what is desirable and what is practicable.

In summarizing the existing situation, the Waterlow Report first considered the current nutritional status of the Jamaican people and then analyzed food supplies and patterns of food consumption. The Report's data provided criteria by which to judge existing food policy and schemes for nutritional improvement. From these conclusions it was possible to go on to examine aspects of research and development, and the feasibility of various strategies to prevent infant malnutrition. The Report, as one would expect of a document drawn up for presentation to a scientific research council, made a clear distinction between facts and inference. Its publication will thus not only provide a baseline for comparisons to be made in the future and a powerful stimulus to other scientific groups to interest themselves in the problem of malnutrition, but also a spur to political discussion and action.

The Waterlow Report was directed to the Jamaican Government and was therefore concerned with economic and social policy. For other target audiences (for example general practitioners, infant welfare staff, health visi-

[1] I am indebted to Prof. J. C. Waterlow for making the nonconfidential material in this Report available to me and for permission to quote from his preface.

tors, pediatricians, or educators) different problems need to be highlighted and different strategies employed. The task of making relevant knowledge available to professional people is one that cannot be left to the journalist; to write a manual on infant feeding or the management of the severely ill child in the hospital is no task for a layman. The involvement of doctors or scientists is necessary. At all events, it is through reportorial activities such as those of the Nutrition Advisory Committee that many scientists are likely to make their most direct and effective contribution to society.

Making Full Use of Scientific Resources

A second way in which scientists could contribute more effectively to social policy than they commonly do is through the addition, to research units and groups, of components that are expressly concerned with current social problems, or with operational research, or with the implications of research findings in particular fields for education or medical practice. Sometimes extra staff or facilities may be needed to enable those engaged in research to increase the scope of their inquiries. They may for example have to collect extra data during a survey, or undertake further analyses of data collected for another purpose; collaboration may need to be sought from colleagues in other disciplines to enable additional projects to be grafted on to a research program; representations to the government and perhaps collaboration with government agencies may enable statistical returns to be better designed or reanalyzed; they may find it possible to share facilities with or give advice to other research groups; they may hold interdisciplinary meetings, or engage in advanced teaching.

That such activities are desirable would seem too obvious to labor were it not that all over the world scientists tend to work in isolation even from their colleagues in the same field and certainly from those in other fields and from practitioners. Collaboration between scientists and practitioners is naturally difficult because the practitioner has constantly to make decisions on the basis of inadequate evidence, and psychologically needs to believe in what he is doing. The scientist, on the other hand, is by profession a doubter and a questioner of evidence and current beliefs. But other considerations also interfere. The scientist is apt to see practical problems as mere distractions, while his qualifications and caveats may seem mere irrelevancies to the administrator. Even collaboration among scientists of different disciplines is rarely, in my experience, truly satisfactory; more commonly activities go on in parallel, or researches proceed quite independently for all practical purposes and gain almost nothing from the fact that people working in the same unit or building conduct them. Interdisciplinary seminars are also all too often a flop or a bore.

No one can say exactly why this should be, though of course it may not matter very much in places where there is a wealth of research facilities and endless duplication of research effort. But where people and resources are scarce it is clearly important that they be used effectively—and it is by no means certain that the gains that accrue when scientists work "undistractedly" are always maximal.

Since scientists themselves find it difficult to work together, even when—as is usually the case—they intend to do so and there is good will, those responsible for research strategy might from time to time, when they are considering the funding of research, give attention to problems of collaboration and of utilization of research findings. They might for example persuade a research team to include among its members a behavioral scientist or applied statistician to exploit certain implications of their findings. A subunit concerned with applied problems might be formed; research staff might be used more effectively in teaching or a system of temporary exchanges might be introduced between the research and teaching staff of a university, or the scientific or administrative staff in government. Not all of these actions

would be effective or indeed appropriate in any particular situation. But today we tend to be remarkably unadventurous in trying any of them, chiefly I believe because no one has a primary responsibility to take the initiative in doing so. A recent discussion of the utilization of social science research (*4*) stressed the part that research councils and funding agencies might play in stimulating research units to broaden the scope of their research if they gave them more money. It is a matter of judgment in particular cases how far additions to a research program can be made without destroying the independence and creativity of its scientists. There is no doubt, however, that sometimes such additions would result in disproportionate gains, and the opportunities provided are by no means always used.

The Provision and Evaluation of Services

Medical and social scientists make their most direct contribution to government by advising and assisting in the planning and evaluation of services. The contribution to public health made by epidemiology has already been mentioned. Gruenberg (*2*) has pointed out that surveys of the incidence and prevalence of diseases or disorders in a community can provide quantitative information to (1) estimate the size, nature, and location of the community's problems, (2) identify the components of the problem, (3) locate populations at special risk of being affected, and (4) identify opportunities for preventive work and needs for treatment and special services. Thus, he says, epidemiology serves as a diagnostician for the official or community leader who is practicing community medicine, social medicine, public health, or public welfare. The nature of the community's health problems is approached diagnostically with epidemiologic methods.

He adds that there are dangers in such community diagnosis surveys. One danger is that of overgeneralization. Another is that: "The motives of those encouraging and financing such studies are not always confined to getting information so as to produce better services more appropriate to the needs of the population. Expensive as surveys are, they are a good bit cheaper than services to sick people, so that this type of research is particularly vulnerable to misuse on the part of those who are opposed to extensions of service and are using the 'need for more information' as a delaying tactic in the political arena." Gruenberg gives the investigator who is caught in this trap a useful tip. He points out that there is enough information already available about unmet needs to go ahead with service planning, without awaiting a new study's results since anyone acquainted with the field can roughly predict them. However, he adds, "this cannot be said about judgments regarding the efficacy of services when they have not been systematically studied previously."

Until comparatively recently the need for evaluative study was barely appreciated. Instead, the view was taken that the provision of services to needy people was in itself likely to benefit them. Given a necessary minimum of competence and sophistication on the part of a service's recipients, this view is a very reasonable one. A failure to monitor the quality of a service can lead to disastrous consequences, however. Thomson (*5*) tells us that in one West African village, recipients know dried milk as "the stuff which causes diarrhea," and Birch and Gussow (*1*) give similar examples from this hemisphere. The Waterlow Report mentions that skimmed milk powder is distributed in Jamaica in 2 kg packs which carry no instructions as to how the powder should be used, nor indeed is there any monitoring of the way it is used. Others have cited instances in which relief organizations have provided dietary supplementation and then withdrawn their help suddenly, creating a situation in which catastrophe is inevitable. No form of intervention is more foolish and tragic than the giving of tractors to people who are

not taught how to use and maintain them, or even that they require maintenance.

At the most general level, however, no one can doubt that better feeding is desirable. Uncertainties relate to the effectiveness of various services, the possibilities of improvement in services, satisfactory methods of introducing new forms of care and education, and alternative ways of providing services. The research worker can help resolve these problems in a number of ways:

He can devise ways to monitor health and education services, developing indicators through which medical and social evaluation can be carried out. The "centers of excellence" in which research is carried out (for example the Mexican village in which Dr. Cravioto's team works, and the Tropical Metabolism Research Unit in the University of the West Indies) can have their educative as well as their research role fully utilized.

Equally important, research on many different patterns of care can be undertaken on a small scale, but its results may lead to a choice of one or other alternatives usable on a wider scale. Experience so gained before national campaigns are feasible or undertaken may enable great savings to be made at a later date.

The professional is often in a better position than others to give advice, provided he informs himself of the situation's everyday realities before doing so. The administrator is always working against pressure of time and a multiplicity of other commitments, and even the professional adviser to a government may not be really an expert, or may have time only to decide how the conventional wisdom may be adapted to the idiosyncrasies of the local situation.

In recommending the involvement of scientists in government, I am not suggesting that it is the job of the expert to make political decisions. He may instead present a series of alternative strategies with arguments in favor and against each, expecting that the administrator will seek alternative sources of advice. It is to be hoped that this does happen: the expert is often wrong. Furthermore the politician must come to a decision on political rather than on merely scientific grounds. Finally, the scientist should not allow himself to be put in the position of being asked whether money spent on health services is more or less well spent than money spent on education, for example. The cost-benefit approach to the provision of services is always of dubious value, and in any case to counterpose health and education in this way seems politically naïve. For one thing, ministries tend to be remarkably independent, one not knowing what others are up to. More important, it seems likely that work done in one field is more rather than less likely to produce activity on the part of a ministry concerned with related fields. In the United States and in Britain, for example, the recent increase in activity in preschool education has brought about a growing awareness of the problems of child poverty and child health, and has stimulated rather than inhibited the development of health and welfare services. Scientists who investigate important social questions and who demonstrate that steps can be taken to solve them can be most effective agents of social change.

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SUMMARY OF SESSION VI

Robert Cook[1]

Dr. Tizard began the session by outlining four obstacles or difficulties in respect of the contributions that scientists can make to recommendations for practical action arising from their research findings: (1) traces exist still of an earlier attitude that science was a thing of purity and should not concern itself too much as to the consequences of its discoveries: (2) some scientists are diffident, feeling that the social and administrative actions in such fields as nutrition and education are of such enormous complexity that they cannot contribute any useful opinions at all; (3) other scientists —and this applies especially to social scientists —think that a total political and social revolution is required in developing countries and that any attempt to ameliorate the social condition of the people without revolution is merely tinkering with the problems, and finally (4), some scientists become, with inadequate background knowledge, hobby horse-riding purveyors of universal panaceas. Only the second obstacle was significant in the subsequent discussion.

Dr. Tizard's conclusion was that the scientists' most useful contributions are provision of information that influences professional and public opinion (the general reviews of topics are most valuable in this respect), and the evaluation of both the baseline situation and the results obtained by projects such as those in nutrition. This evaluation of the effectiveness of services and of alternative methods of providing them was most important and should be undertaken much more than now. The projects set up by scientists in their research could sometimes also be of use in providing pilot projects for wider adoption and application. Dr. Tizard warned, however, that we ought never to allow the lack of field trials to obstruct the provision of services. This, one might add, must certainly be true, for in Britain and elsewhere there might have been great delay in the establishment of child welfare clinics, a revolutionary instrument of change in the early 1900's, had the local and national governments of the time waited for evaluation through field trials.

The Chairman then opened the discussion, asking what guidance could be obtained from the information presented during the conference. He thought that three main topics arose from Dr. Tizard's presentation: epidemiologic research, provision of factual material and advice, and the design of action programs.

The discussion did indeed follow along those lines:

Epidemiologic Research

All agreed that the diagnosis of the situation had to be much wider than just a health diagnosis. The need for all kinds of information input from agriculture, education, trade and industry, finance, and other fields was well recognized.

The opinions of members of the community itself were most important in respect of original diagnosis, but as Miss Fox pointed out, the more one probed for these opinions, the more one realized what a lot of misunderstanding there was between scientists and, say, the mother of an infant.

The point was raised that it was in the very countries where there was the most malnutrition that laboratory facilities to handle investigations were scarcest. One way round this

[1] Caribbean Food and Nutrition Institute, University of the West Indies, Mona, Jamaica.

difficulty, however, would be agreements between local institutions and a university department in an industrialized country.

Provision of Factual Material and Advice

The common interpretation by the professions of the gist of the proceedings of the 1967 M.I.T. conference on malnutrition, learning, and behavior was that a child who was severely malnourished in early childhood might face a serious danger of losing inherited mental potential. This was a fair interpretation and made quite an impact on policy makers all the way up to Robert S. McNamara and his World Bank group. What has this meeting to add to that? In short, it was this:

1. There has been a consistent demonstration at the animal-experiment level that various degrees of malnutrition applied at critical periods resulted in permanent alteration—both deficit and distortion—in brain anatomy, physiology, and biochemistry.

2. At the human level, where there were other significant social disadvantages concurrent with malnutrition, the consequences to the disadvantaged were more severe—an impairment both in mental ability and in behavior. The precise mode and degree of interaction of malnutrition with other social disadvantages is not known, but this is no reason to lessen our concern about the importance of improving nutrition in early childhood. Our index of suspicion, or index of informed concern, about the effects of protein-calorie malnutrition in this respect should be at least as great as our index of concern about birth injuries.

3. It was emphasized again that the effect on behavioral functions could be of major importance.

Design of Action Programs

Dr. Picou asked what means of rehabilitation we proposed for those children who pass through a period of severe protein-calorie malnutrition? In Jamaica they number about 3 per cent of the child population, and it is known for certain that in other countries even point prevalence surpasses this and that the incidence during the first two or three years of life is therefore much higher.

There was one aspect of development in Jamaica that created hope. Public demand for "basic schools" (nursery schools and kindergartens) was very strong, and the groups promoting this movement very lively. It was foreseeable that children aged four through six would receive more educational stimulation. Care should also be taken to meet the children's nutritional needs as much as possible through lunch at school. The program of Drs. Leonardo Sinisterra, and Harrison and Arlene McKay in Cali, Colombia, is an excellent example in this respect, and Chile hopes to follow this pattern on a national scale. That still leaves children under four, who now can be reached only by the maternal and child health services. The findings of this conference underline the tremendous need in all developing countries for an increase in the coverage and and improvement in the quality of maternal and child health services. Dr. Jelliffe thought that attempts to preserve breast-feeding in particular cultures deserved endorsement in the context of this conference.

Dr. Richardson said that there were many lessons that could be learned about nutritional and educational intervention programs, whether in a community or institutional setting. Head Start was an example. Another body of knowledge that tended to be neglected in the design of action programs was that provided by social anthropologists studying the reasons for failure of programs that had at first seemed to be very reasonably conceived.

Miss Fox concluded with the observation that in evaluating action programs to improve design, we should make a practical distinction between programs already existing and programs set up for the specific purpose of operational research.

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